Antibody-Mediated Alphavirus Immunity

Subjects: Infectious Diseases
Contributor: Lisa F.P. Ng

Alphaviruses are mosquito-borne pathogens distributed worldwide in tropical and temperate areas causing a wide range of symptoms ranging from inflammatory arthritis-like manifestations to the induction of encephalitis in humans. Historically, large outbreaks in susceptible populations have been recorded followed by the development of protective long-lasting antibody responses suggesting a potential advantageous role for a vaccine.

Keywords: alphavirus ; antibody ; immunity ; alphavirus vaccine

1. Introduction

Mosquito-borne alphaviruses are Group IV viruses that belong to the family Togaviridae [1]. They are enveloped, positive-sense, single-stranded RNA viruses with a size of ≈70 nm bearing a ≈11.7 kilobases genome which encodes four non-structural proteins (nsP1, nsP2, nsP3 and nsP4) that serve as the virus' replication machinery, and five structural proteins (capsid, E3, E2, 6K and E1) that participate in the envelope assembly process [1]. Clinically, alphavirus infections in humans results in the development of viremia followed by an onset of febrile symptoms [2]. The development of inflammatory conditions compromising joints and muscle tissues has been associated to arthritogenic alphaviruses such as chikungunya virus (CHIKV), O'nyong nyong virus (ONNV), Mayaro virus (MAYV), Ross River virus (RRV), Semliki Forest virus (SFV) and Sindbis virus (SINV) with records of persistent polyarthralgia in a fraction of patients. Conversely, neurotropic alphaviruses such as Eastern Equine Encephalitis virus (EEEV), Western Equine Encephalitis virus (WEEV) and Venezuelan Equine Encephalitis virus (EEEV) have been linked to the induction of lethal encephalitis in humans and animals [3][4].

Historically, alphaviruses have a proven record of causing massive outbreaks in susceptible populations [5][6][7][8]. Additionally, the appearance of mutations favoring their ecological fit to new vectors has fueled alphavirus propagation worldwide [9][10]. A clear example of their potential as a health threat is the re-emergence of CHIKV in 2004 after a hiatus of more than 50 years since its discovery [5]. More recently, tropical emerging alphaviruses such as ONNV and MAYV are believed to have the potential to become future major epidemics [11][12][13]. This is due, in part, to the lack of robust diagnostic tests to differentiate alphavirus infections from other febrile tropical diseases and the absence of continuous epidemiological surveillance masking their real potential for spread beyond endemic areas [14][15][16].

Although alphavirus infections are generally not life threating the economic and social costs incurred during outbreaks are thought to be high [17][18][19]. Moreover, the lack of approved treatments leaves management of alphavirus infections to supportive care [20]. Interestingly, a body of work suggests that the alphavirus infection triggers potent humoral responses in exposed populations which seem to confer protection against re-infection [21]. Therefore, a better understanding of the antibody responses against alphaviruses is crucial for the development of vaccines, which would represent a big advantage in the control of alphavirus infections.

2. Antibody-Mediated Alphavirus Immunity

2.1. Virus-Specific Antibody Kinetics Upon Natural Infection with Alphaviruses

The current knowledge on the role of antibody-mediated immunity upon viral infection has been gathered from cohort studies following major alphavirus outbreaks. Serological surveys following CHIKV re-emergence in 2004 reported the quick development of IgM responses between five to seven days post-illness onset (PIO) [22][23]. IgM is generally detectable for up to three months post-infection [24][25][26]. However, long-lasting IgM has been often reported in patients with long-term CHIKV-induced polyarthralgia, which might indicate a constant antigenic stimulation due to viral persistence [27]. After the initial detection of IgM antibodies, IgG seroconversion reportedly occurs between 4 to 10 days PIO taking over as the main immunoglobulin detected in serum [22][28]. Notably, IgG3 antibodies become the dominant IgG subtype produced upon infection and have been associated to efficient viral clearance and protection against chronic CHIKV symptoms [23]. Importantly, IgG responses persist for several years and might be potentially lifelong [29].

ONNV and MAYV, both closely-related to CHIKV, are re-emerging arthritogenic alphaviruses believed to be confined to sub-Saharan Africa, and Latin America, respectively [6][11][12][15]. Following the largest ONNV outbreak in Uganda involving more than two million cases between 1959–1962 [6][30], the induction of potent neutralizing antibodies was described [31]. The first study cohort that evaluated IgM kinetics upon ONNV infection in Uganda [32] reported the appearance of IgM

antibodies during the second week PIO which remained elevated for two months. In contrast, reports from imported ONNV cases in Europe described detectable IgM levels as early as five days PIO [33][34]. ONNV-specific IgG levels are increased in serum after the third week and remain high beyond two months PIO [11][34]. However, whether IgG responses are long-lasting remains unknown. Similarly, endemic MAYV infections are characterized by the early appearance of IgM antibodies (3–8 days PIO) that might last for one to three months [35][36]. IgG becomes detectable around 4–10 days PIO [35] and remains elevated after 6–12 months [37][38]. Interestingly, unlike ONNV and CHIKV infections, persistent arthralgia has been reported in more than half of MAYV-infected individuals and although MAYV-specific antibody responses are critical for disease resolution it is seemingly insufficient to protect patients from the development of chronic joint manifestations [39].

Other alphaviruses linked to continuous small outbreaks associated with arthritic manifestations in human populations are RRV and SINV. RRV is endemic to Australia and is responsible for approximately 4000–5000 cases annually [40]. Typically, antibody kinetics upon RRV infection are characterized by the development of IgM titers between 7–10 days PIO, peaking at two to three weeks and lasting for 1–3 months [41][42]. IgM response rapidly declines after three weeks PIO as IgG becomes dominant [42][43]. Interestingly, IgM persistence has been reported in some RRV cohorts [41]. In one study [44], 19/116 (16.4%) of participants had detectable IgM levels that lasted between seven months to eight years PIO. Likewise, less prevalent SINV has also been linked to the development of persistent virus-specific IgM levels. Although, generally, the antibody response upon SINV infection generates IgM antibodies after 6–9 days PIO and IgG antibodies after 9–14 days, some reports described the presence of detectable IgM levels up to four years suggesting active viral replication [45][46][47]. The clinical relevance of persistent IgM levels following RRV and SINV infection is yet to be determined.

Neurotropic alphaviruses such as EEEV, WEEV and VEEV cause sporadic cases of human encephalitis in the Americas [4]. While the natural reservoirs for these viruses are primarily birds and equines, humans are susceptible to infection when the enzootic cycle of transmission leaks into mosquito populations with a wide range of hosts [48]. Given that human cases are rare, there is a lack of information regarding the development of antibody responses upon natural infections by neurotropic alphaviruses. In a paired serology study [49], virus-specific antibody responses were profiled in a cohort of 20 EEEV and 17 WEEV-infected patients. IgM antibodies were observed as early as 1 PIO, peaking after 1–2 weeks and remaining detectable for up to three months. In contrast, IgG responses appeared during the second week PIO and remained elevated until the end of the follow-up period.

2.2. Experimental Evidence of the Role of Antibodies in Alphavirus Immunity

To better understand the role of antibody-mediated immunity upon alphavirus infection, several animal models have been used allowing the detailed examination of the cellular compartments responsible for the initiation of humoral immunity. The role of B cells in alphavirus immunity has been described in experimental CHIKV infections. Inoculation of µMT mice (lacking mature B cells) with CHIKV resulted in higher viremia that persisted up to 402 days post-infection (DPI). In contrast, infected wild type (WT) mice were able to control the virus during the second week post-inoculation [50]. Similar findings were reported in other studies, where mouse strains lacking B cells (µMT, Rag1, Rag2/IL2rg, NRG) infected with CHIKV displayed increased and persistent viremia for up to 515 DPI [51][52].

B cells also play an important role in alphavirus-induced encephalitis. Although SINV infections in humans are known to cause arthritic manifestations, SINV has been frequently used as a model of alphavirus-induced encephalomyelitis in adult immunocompetent mice given the virus ability to infect neurons [53]. Intracerebral inoculation of SINV in µMT and severe combined immunodeficiency (SCID) mice resulted in defective viral clearance from the brain, brain stem and lumbar spinal cord, virus persistence and recrudescence compared to WT mice [54]. The individual contributions of IgM and IgG antibodies to SINV clearance from brain tissues were assessed in another study [55] where infection in $AID^{-/-}$ (unable to produce IgG), $sIgM^{-/-}$ (unable to produce IgM) and $AID^{-/-}$ $sIgM^{-/-}$ double-knockout mice resulted only in $AID^{-/-}$ $sIgM^{-/-}$ being unable to control infection efficiently suggesting that either IgM or IgG antibodies are sufficient to clear SINV from the central nervous system (CNS). Similar results were obtained in SFV models of encephalitis where infection of µMT [56], SCID [57] and nude mice with impaired antibody switching [58] led to viral persistence.

Infiltrating virus-specific B cells were observed in infected tissues in a murine model of SINV-induced encephalitis [59][60]. Following intracranial virus inoculation, expansion of IgM-secreting plasmablasts was reported in the cervical lymph nodes. Infiltration of CD19+ B cells occurred between 3–7 DPI and coincided with the starting of viral clearance. During the clearance of persistent viral RNA (from 8–80 DPI), the accumulation of SINV-specific IgG and IgA-secreting B cells was observed being associated with increased SINV antibody titers over time [60]. In a subsequent study, it was reported that the brain microenvironment during the early stages of SINV infection facilitates the migration, differentiation, expansion and long term survival of SINV-specific B cells [59].

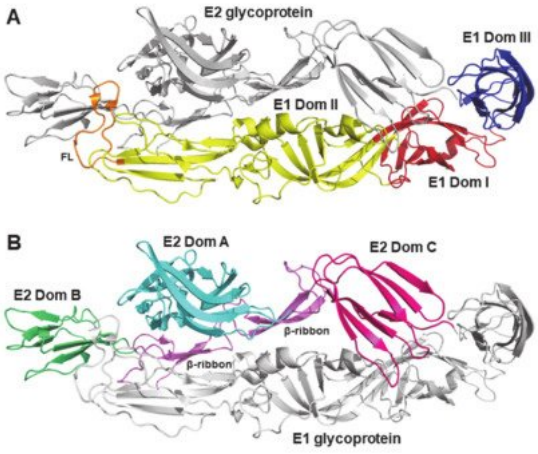
Follicular helper T cells (T_{FH}) are a subset of CD4 T cells involved in the activation of B lymphocytes and the establishment of robust antibody responses following antigen stimulation. T_{FH} promotes B cell differentiation, isotype switching and affinity maturation. In experimental CHIKV infections, the use of CD4-deficient mice ruled out the role of CD4 T cells in viral clearance from infected tissues [61]. However, one study demonstrated impaired IgM and IgG (IgG2c, IgG1, and IgG2b) production in mice lacking CD4 T cells following CHIKV inoculation [62]. Albeit reduced virus-specific

antibody levels, the neutralizing capacity of sera from virus-infected CD4-deficient mice was marginally affected [62]. Likewise, another study showed similar results upon CHIKV inoculation of MHCII$^{\Delta/\Delta}$ mice (defective of T_{FH}) [51]. MHCII$^{\Delta/\Delta}$ animals were unable to generate IgG1 antibodies and produced ≈100 fold lower IgG2c levels than WT controls. Nonetheless, MHCII$^{\Delta/\Delta}$ mice were still able to control virus infection [51]. The generation of virus-specific neutralizing antibodies in MHCII$^{\Delta/\Delta}$ mice suggests a T-cell independent B cell activation characterized by the inability to generate memory B cells. Whether CHIKV-specific antibody responses in mice lacking CD4 T cells are long-lasting remains to be elucidated.

2.3. Viral Antigenic Regions Targeted by Neutralizing Antibodies

The notion of targeting humoral immunity as a therapy against alphavirus infection has been investigated since the late 1930s following the isolation of EEEV, WEEV and VEEV. In a series of seminal studies involving immunization of guinea pigs [63][64][65][66], the subcutaneous inoculation of live EEEV and WEEV strains protected guinea pigs from lethal intracranial infection [63]. Additionally, it was observed that immunization with formalin-inactivated virus strains induced the production of neutralizing antibodies at a comparable level than animals immunized with live viruses [64][65][66]. Subsequent studies reported that passive transfer of hyperimmune rabbit serum protected mice, guinea pigs and rabbits from WEEV infection [66][67]. Similarly, passive serum transfer was shown to be effective at protecting mice from the development of neurological complications upon infection with a neuroadapted strain of SINV [68][69]. Comparable observations were reported in experimental infection models of VEEV [70], CHIKV [71][72], RRV [73] and SFV [74].

The first attempts in identifying the exact structural regions, recognized by most neutralizing antibodies produced upon infection, were conducted in experimental infection models of alphavirus encephalitis. Structurally, the envelope of an alphavirus virion has a T = 4 icosahedral symmetry [75]. E1 and E2 are two envelop surface glycoproteins exposed in the viral spike as a heterodimer [75] (Figure 1). It is believed that the E1-E2 heterodimer interacts with host receptors thus mediating viral entry [75]. Additionally, the E1 and E2 glycoproteins were postulated as highly immunogenic regions since their location in the spike facilitates antigenic recognition. In line with this, early works mapped antigenic sites involved in VEEV, SINV and SFV neutralization to the E1 and E2 proteins using competitive binding assays but the exact amino acid sequences were not determined [76][77][78]. Later, a major antigenic region involving three epitopes important in the neutralization of RRV was identified in the E2 protein (incorporating residues 216, 232 and 234) [79]. Similarly, analysis of antibody escape variants determined important antigenic regions between amino acids 181 and 216 on the E2 protein of SINV [80]. A major neutralization domain was also identified between residues 182–207 for VEEV [81].



C

	E1 glycoprotein			E2 glycoprotein		
	Dom I	Dom II	Dom III	Dom A	Dom B	Dom C
CHIKV		92		23, 90-92	90-92, 98	91
ONNV						
MAYV		103			103	
RRV				102	79, 102	
SINV		83			80	83
EEEV				99, 101	99, 101	
WEEV				81		
VEEV					81	

Figure 1. Structure of the alphavirus E1-E2 heterodimer. Ribbon diagram (PDB: 3N41) highlighting (**A**) E1 glycoprotein (domain I: red, domain II: yellow, domain III: blue, fusion loop FL: orange, E2: grey) and (**B**) E2 glycoprotein (domain A: cyan, domain B: green, domain C: pink, beta-ribbons: purple, E1: grey). (**C**) Table summarizing reported antibody binding regions in the E1 and E2 glycoproteins of arthrogenic and neurotropic alphaviruses. Numbers in the table refer to in-text citations describing such binding sites (See Reference list). Background color matches protein doimains depicted in (**A**) and (**B**). To assess for the degree of conservation among common antigenic regions across alphaviruses a sequence aligment analysis was conducted.

Following CHIKV reemergence in 2004 several reports identified major linear antigenic sites in the CHIKV E2 protein that induced the production of potent neutralizing antibodies. Using a CHIKV proteome-wide screening approach, a single

linear peptide located at the N-terminus of the E2 glycoprotein, E2EP3, was reported as strongly recognized by convalescent CHIKV patients from different cohorts [23]. Furthermore, experimental CHIKV infection in mice and non-human primates (NHP) validated E2EP3 as an immunodominant linear epitope inducing potent neutralizing antibodies [23][62][82]. Interestingly, mice immunization with E2EP3 alone reduced joint swelling and viremia upon CHIKV challenge [23]. In another study focusing on human antibody responses to SINV in cohort from Finland, 6 linear epitopes, located in the capsid, E2, E1 and PE2 (uncleaved E3-E2) proteins, were reported [83]. Three of these epitopes were located to the glycoprotein spike complex between the residues 209–226 of E1 (E1-P5), 273–290 (E2-P3) and 308–325 (E2-P4) of E2 [83]. Interestingly, the E2EP3 equivalent of SINV remained non-reactive suggesting that antibody kinetics against linear E2EP3 between populations exposed to CHIKV and SINV might differ [83].

The development of mouse and human monoclonal antibodies against different alphaviruses helped further the understanding of antigenic responses upon infection by the identification of conformational epitopes. Early works have shown the therapeutic value of mouse monoclonal antibodies in models of alphavirus encephalitis by SINV [84][85][86][87][88], SFV [56][57][89] and VEEV [78]. Interestingly, it was observed that neutralizing monoclonal antibodies target antigenic regions in the E2 protein. Whereas, non-neutralizing antibodies bind to the E1 protein, yet both are able to confer protection upon alphavirus infection, thereby suggesting other mechanisms of protection in vivo besides virus neutralization [48]. Several monoclonal antibodies targeting both E1 and E2 proteins have been reported in the context of arthritogenic alphavirus infection. Mouse monoclonal antibodies targeting the A and B domain of E2 and the domain II of E1 [90][91][92] and the capsid protein [93][94] have been reported for CHIKV. Likewise, human anti-CHIKV monoclonal antibodies were found to target conformation epitopes in the E2 glycoprotein A (containing a putative RBD [95]) and B (shielding the fusion loop in E1 [96]) domains and proved therapeutic value in experimental NHP infections [90][97][98]. Monoclonal antibodies recognizing epitopes predominantly between residues 58–80 (domains A) or residues 180–215 (domain B) of the E2 glycoprotein have been also reported in the context of SINV [83], VEEV [81], EEEV [99][100][101], RRV [102] and MAYV [103].

The combined evidence suggested the existence of common antigenic sites in the viral spike across alphaviruses, particularly in the E2 protein. These sites are likely required for interaction with host cell receptors suggesting that antibody binding might inhibit infection during viral attachment, entry, fusion or egress [90]. In line with this, a recent study reported the discovery of Mxra8, a cell adhesion molecule, as a host receptor required for viral entry of multiple arthritogenic alphaviruses [104]. Genetically altering mouse or human Mxra8 resulted in diminished infection, conversely, overexpression of Mxra8 in cell lines increased infection rates by CHIKV, ONNV, MAYV and RRV [104][105]. Interestingly, mutagenesis experiments suggested E2 domains A and B as the putative binding site for Mxra8 [104]. This notion was later confirmed by cryo-electron microscopy images of Mxra8 bound to CHIKV [106][107]. Mxra8 sits onto a cleft formed by two contiguous CHIKV E2-E1 heterodimers in one trimeric spike while engaging a neighboring spike [106]. It is believed that this interaction works against the virus by obstructing viral fusion [106]. Importantly, human neutralizing antibodies that recognize regions of the A domain of E2 inhibited the binding of Mxra8 supporting the interactions determined in the cryo-EM atomic model. Notably, Mxra8 seems to not be a receptor for neurotropic alphaviruses [104]. The alignment of CHIKV residues involved in Mxra8 binding reveled a degree of conservation in arthritogenic alphaviruses (44%), but diverged from neurotropic Alphaviruses (14%) which might explain the negative results in the context of SINV, EEEV, WEEV and VEEV infections [106]. In summary, the characterization of alphavirus antigenic epitopes has proven beneficial to pave the way for the development of antibody therapies and vaccines.

3. Alphavirus Vaccine Development

Recent decades have seen increased rates of geographic dispersal of arboviral re-emergence, due to factors such as growth of global transportation, urbanization and failure of mosquito control [108][109][110][111]. Given that humans appear to be the only amplification hosts and viral reservoir during urban transmission [112][113], another effective means of controlling the spread of infection is through vaccination. While there are currently no licensed or approved vaccines available for alphaviruses, a multitude of approaches have been used to develop vaccine candidates capable of, not only generating high levels of antibodies, but also providing long-lasting protection, with the ease of administration and production requirements. Multiple methods such as live-attenuated viruses, inactivated viruses, virus-like particles (VLP), recombinant subunit vaccines and chimeric vaccines have been explored for vaccine options (Figure 2 and Table 1).

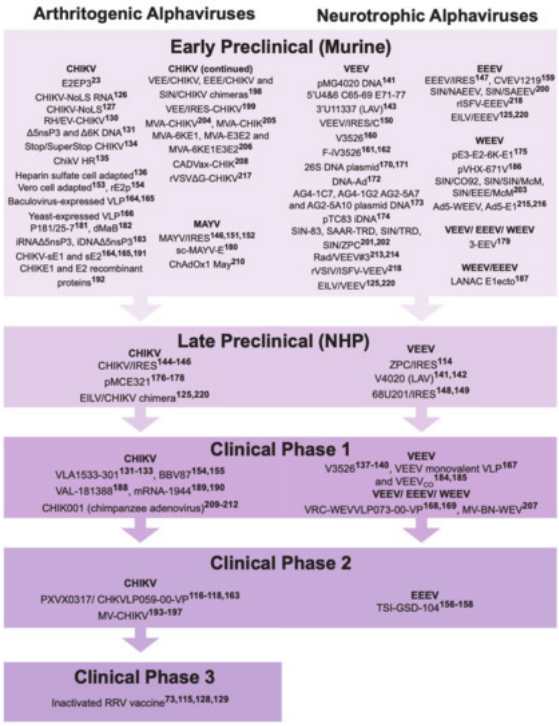


Figure 2. An outline of the current vaccine options against arthritogenic (left panel) and neurotropic (right panel) alphaviruses. Most of these vaccine candidates are currently under preclinical testing (early preclinical—vaccine candidates tested in mouse models; late preclinical—vaccine candidates currently under testing in non-human primates (NHP)), while a minority of them are currently undergoing clinical trials (Phase 1, 2 or 3). LAV; live-attenuated virus; VLP, virus-like particle; SIN, Sindbis virus; ISFV, Isfahan virus; May, Mayaro virus; EILV, Eilat virus, VSV/VSIV, vesicular stomatitis virus; MV, measles virus; MVA, modified vaccinia virus Ankara. Data curated from literature reported through February 2021. Numbers in superscript refer to reference numbers (See Reference list [23][73][114][115][116][117][118][119][120][126][127][130][131][134][135][136][141][142][143][144][145][146][147][148][149][150][151][152][153][154][156][157][158][159][160][161][162][163][164][165][166][167][168][169][170][171][172][173][174][175][176][177][178][179][180][181][182][183][184][185][186][187][188][189][190][191][192][193][194][195][196][197][198][199][200][201][202][203][204][205][206][207][208][209][210][211][212][213][214][215][216][217][218][219][220]).

Table 1. List of vaccine candidates against relevant alphaviruses currently under development [1].

Vaccine Against Virus	Name	Strain Vaccine Modelled After	Phase	Immunization			Challenge	
				Dose	Route	Schedule	Dose (Strain, Genotype)	F
	Live-attenuated							
CHIKV, ONNV	RH-CHIKV EV-CHIKV RHEV-CHIKV	LR2006 OPY1	C57BL/6 mice, 3 week old	10^6 PFU	s.c. in the ventral side of the right hind footpad	Single dose	10^6 PFU LR2006 OPY1 or WT-ONNV IMTSSA/5163, 3 mpim	V

Vaccine Against Virus	Name	Strain Vaccine Modelled After	Phase	Immunization			Challenge	
				Dose	Route	Schedule	Dose (Strain, Genotype)	F
CHIKV	Δ5nsP3 (VLA1553-301 in clinical trials) and Δ6K	LR2006 OPY1	C57BL/6 mice, 5 to 6 week old	10^4 or 10^5 PFU	s.c. in both flanks	Single dose	10^6 PFU LR2006 OPY1, 7 wpim	
			Cynomolgus macaques, 3–4 years old	10^5 PFU	s.c. in the right upper back side	Single dose	100 AID50 (corresponding to 7000–10,000 PFU) LR2006 OPY1, 123 dpim	
			Human clinical trial, Phase 1	3.2×10^3, 3.2×10^4 or 3.2×10^5 TCID50	i.m.	Two doses (0 and 6 months, or 0 and 12 months)	NA	
CHIKV	CHIKV-NoLS	LR2006 OPY1	C57BL/6 mice, 21 days of age	10^4 PFU	s.c.	Single dose	10^4 PFU of LR2006 OPY1 or Ross River virus, 30 dpim	
CHIKV	Stop CHIKV SuperStop CHIKV	LR2006 OPY1	C57BL/6 mice, 5 week old	10^4 PFU	s.c.	Single dose	ND	
CHIKV	ChikV HR	37997	C57BL/6 mice, 28 days of age	~10^3 PFU	s.c. into the left footpad	Single dose	10^3 PFU CHIKV SL15649, 28 dpim	
CHIKV	Heparin sulfate cell culture adapted	LR2006 OPY1	CD-1 mice, 21 days old	10^5 GE	s.c. in the rear footpad	Single dose	10^3 PFU LR2006 OPY1, 21 dpim	

Vaccine Against Virus	Name	Strain Vaccine Modelled After	Phase	Immunization			Challenge	
				Dose	Route	Schedule	Dose (Strain, Genotype)	F
VEEV	V3526	IA/B Trinidad donkey	BALB/c, 6 to 8 week oldC3H/HeN mice, 6 to 8 week old	10^5 PFU	s.c.	Single dose	10^5 PFU of TrD, 28 dpim	
			Cynomolgus macaques (age not specified)	2.5×10^6 PFU	s.c.	Single dose	~10^8 PFU VEEV IE 68U201, 8 wpim	
			Rhesus macaques (2 to 4 years old)	1.3×10^5 or 7.5×10^4 PFU	s.c. or i.t./i.s.	Single dose	ND	
			Human clinical trial, Phase 1	25 or 125 PFU	s.c.	Single dose	NA	
VEEV	V4020	IA/B Trinidad donkey	BALB/c mice, 4 to 8 week old	10^4 PFU	s.c.	Single dose	10^4 PFU of VEEV TrD, 28 dpim	
			Cynomolgus macaques (age not specified)	~10^4 PFU	s.c. in the right leg	Single dose (or second dose at 2 x 10^4 PFU i.m. if did not seroconvert)	10^6 to 10^7 PFU of the VEEV TrD, 73 dpim	
EEEV	5′U4&6 C65-69 E71-77 3′U11337 mutants	FL93-939	CD-1 mice, 5 to 6 week old	1.5×10^5 GE	s.c. in footpad, or i.c.	Single dose	10^5 PFU EEEV FL93, 21 dpim	
Live-attenuated (IRES)								

Vaccine Against Virus	Name	Strain Vaccine Modelled After	Phase	Immunization			Challenge	
				Dose	Route	Schedule	Dose (Strain, Genotype)	F
CHIKV	CHIKV/IRES	LR2006 OPY1	A129 mice, 3 or 10 week old	10^4 PFU	i.d.	Single dose	100 PFU LR2006 OPY1, 94 dpim	
			C57BL/6 mice, 3 week old	10^5 PFU	s.c. in the hind leg	Single dose	$10^{6.5}$ PFU Ross CHIKV, 21 dpim	
			A129 mice, 8 to 10 week old	10^5 TCID50	s.c.	Single dose	100 PFU LR2006 OPY1, 50 dpim	
			Cynomolgus macaques, >3 years old	10^5 PFU	s.c. or i.d.	Single dose	10^5 PFU LR2006 OPY1, 52 dpim	
ONNV	CHIKV/IRES	LR2006 OPY1	A129 mice, 6 to 7 week old	10^4 PFU	i.d.	Single dose	10^5 PFU ONNV SG650, 38 dpim	
VEEV	ZPC/IRESv1, ZPC/IRESv2	ID ZPC738	CD-1 mice, 6 to 8 week old	10^5 PFU	s.c. in the scruff of the back	Single dose	10^5 PFU VEEV 3908, 4 wpim	
			Cynomologous macaques, age not specified	10^5 PFU	s.c. in the upper deltoid	Single dose	~ 8×10^5 to 9×10^6 PFU VEEV 3908, 35 dpim	
EEEV	EEE/IRES	FL93-939	NIH Swiss mice, 3 to 4 week old	10^4 PFU	s.c. in the medial thigh	Single dose	10^3 PFU of FL93-939, 4 wpim	
VEEV	68U201/IRESv1 68U201/IRESv2	IE 68U201	CD1 mice, 6 to 8 week old	10^5 PFU	s.c. in right hind leg	Single dose	(Lethal dose, NP) 68U201 at 1, 3, or 12 mpim	
			Cynomolgus macaques (age not specified)	10^5 PFU	s.c. in the upper deltoid	Single dose	4×10^4 PFU VEEV IE 68U201, 49 dpim	
VEEV	VEEV/IRES/C	IA/B Trinidad donkey	CD-1 mice, 8 week old	10^5 PFU	s.c.	Single dose	10^4 PFU of VEEV 3908, 6 wpim	

Vaccine Against Virus	Name	Strain Vaccine Modelled After	Phase	Immunization			Challenge	
				Dose	Route	Schedule	Dose (Strain, Genotype)	F
MAYV	MAYV/IRES	MAYV-CH	BALB/c, 6 week old	2×10^5 PFU	s.c. i.pl. route	Single dose	2×10^5 PFU of WT MAYV, 28 dpim	s
			AG129	2×10^4, 2×10^3 or 2×10^2 PFU	s.c. i.pl. route	Single dose	2×10^3 PFU of WT MAYV, 14 dpim	s
			CD-1, 28-day old	10^5 PFU	s.c. over the dorsum	Single dose	ND	
			AG129, 5 to 8 week old	10^4 PFU	i.d. on the left foot	Single dose	10^4 PFU of WT MAYV, 29 dpim	
	Inactivated							
CHIKV	Vero cell adapted	DRDE-06	Swiss albino mice, 3 to 4 week old	10, 25 or 50 ug	s.c.	Three doses (0, 14 and 28 days)	ND	
CHIKV	BPL/formalin-inactivated CHIKV	IND-06-AP3	BALB/c mice, 4 to 6 week old	10, 20 or 50 µg	i.m.	Two doses (0 and 14 days)	2.5 x 10^4 TCID50 IND-06-AP3, 4 or 22 wpim	
	BBV87 (in clinical trials)		Human clinical trial, Phase 1	10, 20 or 30 µg	i.m.	Three doses (0, 29 and 57 days)	NA	

Vaccine Against Virus	Name	Strain Vaccine Modelled After	Phase	Immunization			Challenge	
				Dose	Route	Schedule	Dose (Strain, Genotype)	F
RRV	Vero cell culture-derived whole-virus RRV vaccine Ross River Virus (RRV) Vaccine	T48	CD-1 mice, 7 to 8 week old	0.0025, 0.01, 0.039, 0.156, 0.625, 2.5 or 10 µg	s.c.	Two doses (0 and 28 days)	10^6 TCID50 RRV T48, 42 dpim	
			A129 mice, 7 to 8 week old	0.063, 0.25 or 1 µg	i.m.	Two doses (0 and 21 days)	$10^{2.5}$ TCID50 T48, 42 dpim	
			CD-1 mice, age not specified	10 µg	s.c.	Two doses (0 and 28 days)	10^6 TCID50 T48, 6 wpim	
			Guinea pigs (Duncan Hartley), age not specified	10 µg	s.c.	Single or two doses (0 and 6 weeks)	10^6 TCID50 T48, 10 or 34 wpim	
			Human clinical trial, Phase 1/2	1.25, 2.5, 5, or 10 µg	i.m.	Three doses in escalation (0, 21 days, 6 months)	NA	
			Human clinical trial, Phase 3	2.5 ug	i.m.	Three doses (0, 3 weeks, 6 months)	NA	
EEEV	TSI-GSD-104 (formalin inactivated)	PE-6	Human clinical trial, Phase 2	NP	s.c. (0 and 28 days), i.d. (6 months)	Three doses (0, 28 days and 6 months)	NA	
EEEV	fCVEV1219 iCVEV1219 gCVEV1219	CVEV1219	BALB/c mice, 6 to 8 week old	0.1 to 5 µg of inactivated EEEV	i.n., s.c. or i.m.	Single dose or two doses (0 and 28 days)	Lethal dose of EEEV FL93-939, at 28 dpim (single dose) or 56 dpim (two doses)	
VEEV	V3526 virus	V3526	BALB/c mice, 6 week old	0.2 µg (s.c.) or 0.04 µg (i.m.)	s.c. or i.m.	Two doses (0 and 28 days)	10^4 PFU VEEV TrD, 56 dpim	

Vaccine Against Virus	Name	Strain Vaccine Modelled After	Phase	Immunization			Challenge	
				Dose	Route	Schedule	Dose (Strain, Genotype)	F
VEEV	F-iV3526	V3526	BALB/c mice, 8 to 10 weeks old	1, 3 or 5 µg	i.n., s.c. (under the skin over the neck) or i.m. (thigh muscle of the hind leg)	Single dose	454 (i.n.), 897 (i.m.) or 55 (s.c.) PFU VEEV-TrD, 56 dpim	
Virus-like particle								
CHIKV	VRC 311 Or VRC-CHKVLP059-00-VP/ PXVX0317 (in clinical trials)	37997	BALB/c mice, 6 to 8 week old	19 µg	i.m.	2 doses (2 and 5 weeks)	ND	
			Cynomolgus macaques, 3 to 4 years old	20 µg	i.m.	3 doses (0, 4 and 24 weeks)	10^{10} PFU LR2006 OPY1, 15 wpim	
			Human clinical trial, Phase 1	10, 20 or 40 µg	i.m.	3 doses (0, 4 and 24 weeks)	NA	
			Human, clinical trial Phase 2	20 µg	i.m.	2 doses (0 and 28 days)	NA	
			Human clinical trial (Phase 2b, recruitment completed)	6, 10 or 20 µg	NP	Two doses (0 and 14 or 28 days)	NA	
CHIKV	Baculovirus-expressed VLP	S27	AG129, 6 week old	1 µg	s.c.	2 doses (0 and 21 days)	1000 TCID50 S27, 6 wpim	
			C57BL/6 mice, 6 to 12 week old	0.1 or 1 µg	s.c.	Single dose	10^4 $CCID_{50}$ LR2006 OPY1, 6 wpim	
CHIKV	Yeast-expressed VLP	DRDE06/DRDE07	BALB/c mice, 4 week or 2 days old	10, 20 or 40 ug	s.c.	Three doses (0, 14 and 28 days)	ND	
VEEV	Venezuelan Equine Encephalitis Monovalent Virus-Like Particle Vaccine (VEEV)	NA	Human clinical trial (Phase 1, not recruiting)	2, 10, or 20 µg	i.m.	Dose escalation (0, 28 days, and day 140 booster)	NA	

Vaccine Against Virus	Name	Strain Vaccine Modelled After	Phase	Immunization			Challenge	
				Dose	Route	Schedule	Dose (Strain, Genotype)	F
WEEV, EEEV, and VEEV	VRC-WEVVLP073-00-VP (Trivalent vaccine)	WEEV CBA87, EEEV PE-6 and VEEV TC-83	BALB/c mice, 6 to 8 week old	monovalent (5 μg) or trivalent (5 μg each)	i.m.	Two doses (0 and 21 days)	2.5×10^3 PFU WEEV CBA87, 8.9×10^3 PFU EEEV FL93-939, and 1.3×10^3 PFU VEEV Trinidad donkey, 56 dpim	
			Cynomolgus macaques, age not specified	Monovalent (20 μg) or trivalent (20 μg each)	i.m.	Two doses (0 and 28 days)	10^6 PFU WEEV CBA87, 10^8 PFU EEEV FL93-939, and 10^8 VEEV Trinidad donkey, 56 dpim	
			Human clinical trial, Phase 1	6, 30 or 60 μg	i.m.	Dose escalation (0 and 8 weeks)	NA	
DNA/RNA								
VEEV	VEEV 26S DNA plasmid	I/AB TrD	BALB/c mice, 6 to 8 week old	~3 μg	DNA/gene gun, delivered to two sites on the abdomen of each mouse	Three doses (at 3-week intervals)	~10^4 PFU of TrD, 9 wpim	
			Hartley guinea pigs, age not specified	~5 μg	DNA/gene gun, delivered to two sites on the abdomen of each mouse	Three doses (0, 4 and 8 weeks)	~10^4 PFU of TrD, 21 wpim	
VEEV	DNA-Ad	TC-83	BALB/c mice, 6 to 8 week old	1 μg of DNA per dose and 107 PFU of RAd/VEEV #3 per boost	gene guni.n.	immunised with the DNA vaccines on day 0, 14 and 28 and Ad-based vaccine on day 42	100 LD50 of virulent airborne VEEV, 63 dpim	

Vaccine Against Virus	Name	Strain Vaccine Modelled After	Phase	Immunization			Challenge	
				Dose	Route	Schedule	Dose (Strain, Genotype)	F
VEEV	AG4-1C7 AG4-1G2 AG2-5A7 AG2-5A10 plasmid DNA	I/AB TrD	BALB/c mice, 6 to 8 week old	4 µg	particle-mediated epidermal delivery (i.d.)	Three doses (at 3-week intervals)	~10^4 PFU of VEEV TrD (≥1000 LD50), 70 dpim	
VEEV	pTC83 iDNA	TC-83	BALB/c mice, 3 week old	50 µg	i.m. electroporation	Single dose	10^5 PFU VEEV 3908, 21 dpim	
WEEV	pE3-E2-6K-E1 pE3-E2 P6K-E1	71V-1658	BALB/c, age not specified	2 µg	gene gun	Three doses (14 days apart)	1500 PFU WEEV 71V-1658, Fleming, or CBA87, 42 dpim	
CHIKV	pCHIKV-Capsid, pCHIKV-Envelope (pMCE321)	Consensus	C57BL/6 mice, 3 to 4 week old	25 µg, 2–3 times	Electroporation	Two doses (2 weeks apart)	ND	
			C57BL/6 mice, 6 to 8 week old	25 µg	i.m. electroporation	Three doses (0, 14 and 21 days)	7$\log_{10}$ PFU of PC-08, 35 dpim	
			BALB/c mice	25 µg	i.m. electroporation	Two doses (2 weeks apart)	7$\log_{10}$ PFU PC-08	
			Rhesus macaques, age not specified	1 mg	i.m. electroporation	Three doses (4 weeks apart)	ND	
CHIKV	Δ5nsP3 and Δ6K DNA	LR2006 OPY1	C57BL/6 mice, 5 to 6 week old	20 µg	i.d. with DermaVax electroporation	Single dose or two doses (0 and 3 weeks)	10^6 PFU LR2006 OPY1, 7 wpim	

Vaccine Against Virus	Name	Strain Vaccine Modelled After	Phase	Immunization			Challenge	
				Dose	Route	Schedule	Dose (Strain, Genotype)	F
CHIKV	CHIKV-NoLS RNA	LR2006 OPY1	C57BL/6 mice, 28 days of age	2 µg	s.c. in the ventral/lateral side of the right foot	Single dose	10^4 PFU LR2006 OPY1, 30 dpim	V ((
			AG129 mice, 28 days old	2 µg	s.c. in the ventral/lateral side of the right foot	Single dose	10^4 PFU LR2006 OPY1, 30 dpim	V ((
VEEV, WEEV and EEEV	3-EEV	VEEV IAB TrD, WEEV CBA874 and EEEV FL91-46794	C57BL/6 mice, 6 to 8 week old	15 µg	i.m. electroporation	Two doses (0 and 21 days)	10^4 PFU VEEV IAB TrD or 2 × 10^4 PFU WEEV CBA874 or 105 PFU EEEV FL91-46794, 7 wpim	
MAYV	scMAYV-E	NA	C57BL/6 mice, 5 to 8 week old	25 µg	i.m. electroporation	Single, two doses or three doses (at 2 week intervals)	ND	
			A129 mice, 4 to 6 week old	25 µg	i.m. electroporation	Single, two doses or three doses (at 2 week intervals)	10^2 PFU MAYV 15537	
CHIKV	p181/25-7	TSI-GSD-28	BALB/c mice, 3 week old	10 µg	i.m. electroporation	Single dose	6 × 10^6 PFU CHIKV Ross, 28 dpim	
CHIKV	dMaB	NA	BALB/c mice, age not specified	100 µg	Electroporation	Single dose	10^7 PFU Del-03	
CHIKV	iRNAΔ5nsP3 iDNAΔ5nsP3	LR2006 OPY1	C57BL/6 mice, 8 week old	0.125, 1.25 or 10 µg	i.m. in the gastrocnemius muscle of the left hind leg	Single dose	10^6 PFU LR2006 OPY1, 5 wpim	
VEEV	pMG4020 DNA plasmid	TC-83	BALB/c, 4 to 8 week old	0.5 or 5 ug	i.m. electroporation	Single dose	10^4 PFU VEEV TrD, 28 dpim	

Vaccine Against Virus	Name	Strain Vaccine Modelled After	Phase	Immunization			Challenge	
				Dose	Route	Schedule	Dose (Strain, Genotype)	F
VEEV	$VEEV_{WT}$ $VEEV_{COCAP}$ $VEEV_{CO}$	IAB TrD	BALB/c, 6 to 8 week old	25, 5, or 1 µg	i.m. electroporation	Two doses (3 weeks apart)	~10^4 PFU VEEV IAB strain TrD, 7 wpim	
			New Zealand White rabbits, age not specified	500 µg of $VEEV_{CO}$	i.m. electroporation	Three doses (0, 28 and 230 days)	ND	
			Cynomolgus macaques, age not specified	50 or 500 µg of $VEEV_{CO}$	i.m. electroporation	Two doses (0 and 56 days)	3×10^8 PFU VEEV IAB TrD	
			Human clinical trial, Phase 1	0.5 or 2 mg	i.m. electroporation or i.d. electroporation	Three doses (days 0, 28, and 56)	NA	
WEEV	pVHX-671V-1658 pVHX-6 CBA87 pVHX-6 Fleming	Fleming, CBA 87 or 71V-1658,	BALB/c mice, age not specified	2 shots × 2.5 µg precipitated on 0.5 mg gold	gene gun	Four doses (2 weeks apart)	1.5×10^3 PFU WEEV Fleming, CBA 87 or 71V-1658, 8 wpim	
WEEV and EEEV	LANAC E1ecto	WEEV McMillan	CD-1 mice, 4 to 6 week old	10 µg	s.c. injection dorsal to the cervical spine	Two doses (2 weeks apart)	10^4 PFU WEEV McMillan, Montana-64, or EEEV Florida-93, 4, 5, 9, 11, or 13 wpim	
CHIKV	mRNA-1388 (or VAL-181388 in clinical trials)	NA	Human clinical trial, Phase 1	25, 50 or 100 µg	i.m.	Dose escalation procedure (0 and 4 weeks)	ND	

Vaccine Against Virus	Name	Strain Vaccine Modelled After	Phase	Immunization			Challenge	
				Dose	Route	Schedule	Dose (Strain, Genotype)	F
CHIKV	mRNA-1944	SL15649	AG129, age not specified	0.4, 1 or 10 mg/kg	i.v. tail vein injection	Single dose	$10^{2.5}$ TCID50 of CHK	s
			Cynomolgus macaques, 2 to 3 year old	0.5 mg/kg	i.v.	Single dose	ND	
			Human clinical trial, Phase 1 (active, not recruiting)	0.1, 0.3 and 0.6 mg/kg	i.v.	Dose escalation	NA	
Subunit								
CHIKV	CHIKV-sE1 and -sE2	S27	AG129 mice, 6 week old	2 µg	s.c.	Two doses (0 and 21 days)	1000 TCID50 of S27 isolate, 9 wpim	
CHIKV	rE2p	IND-06-AP3	BALB/c, 6 to 8 week old	10, 20 or 50 µg	i.m.	Two doses (2 weeks apart)	Mice immunized with 50 µg challenged with 7 log10 TCID50 /mL, 4 or 22 wpim	
CHIKV	CHIKE1 and CHIKE2 recombinant proteins	DRDE-06	BALB/c	40 µg	s.c.	Three doses (0, 21 and 35 days)	ND	
Chimeric virus								
Measles virus-based chimeras								

Vaccine Against Virus	Name	Strain Vaccine Modelled After	Phase	Immunization			Challenge	
				Dose	Route	Schedule	Dose (Strain, Genotype)	F
CHIKV (VLP)	MV-CHIKV	06–49	CD46-IFNAR, 6 week old	10^3 to 10^5 TCID50	i.p.	Single or two doses (30 days apart)	100 PFU of CHIKV 06-49, 2 mpim	
			Cynomolgus macaques, age not specified	5×10^5 (± 0.5 log) TCID50	i.m.	Two doses (28 days apart)	1.4×10^5 PFU LR2006 OPY1, 56 dpim	
			Human clinical trial, Phase 1	1.5×10^4, 7.5×10^4 or 3.0×10^5 TCID50	i.m. or s.c.	Dose escalation (0 and 28 days, or 0 and 90 days)	NA	
			Human clinical trial, Phase 2	5×10^4 or 5×10^5 TCID50	i.m.	Three doses (0, 28, and 196 days)	NA	
	Alphavirus-based chimeras							
CHIKV	VEE/CHIKV EEE/CHIKV SIN/CHIKV	LR2006 OPY1	NIH Swiss, C57BL/6, >3 week old	5.8 $\log_{10}$ PFU (VEE/CHIKV and SIN/CHIKV), 5.3 $\log_{10}$ PFU (EEE/CHIKV)	s.c. in the medial thigh	Single dose	6.5 $\log_{10}$ PFU (Ross CHIKV strain), 21 dpim	
CHIKV	VEE/IRES-CHIKV VEE/IRES-C/CHIKV	NA	A129 mice, 6 to 9 week old	10^4 PFU	s.c.	Single dose	10^2 PFU of LR2006 OPY1, 5 weeks post immunization	
CHIKV	EILV-CHIKV	CHIKV 996659	C57BL/6 mice, 4 week old	8.8 $\log_{10}$ PFU	s.c.	Single dose	6 $\log_{10}$ PFU 99659, 30 dpim	
			IFNα/βR−/−, 6 week old	8.8 $\log_{10}$ PFU	s.c.	Single dose	3 $\log_{10}$ PFU 99659, 292 dpim	
			Cynomolgus macaques, 3 to 5 years	8.1 $\log_{10}$ PFU	i.m. into the right quadriceps	Single dose	5 $\log_{10}$ PFU LR2006 OPY1, 31 dpim	

Vaccine Against Virus	Name	Strain Vaccine Modelled After	Phase	Immunization			Challenge	
				Dose	Route	Schedule	Dose (Strain, Genotype)	F
EEEV	EILV/EEEV	EEEV FL-93	Adult CD-1 mice (age not specified)	10^8 PFU	s.c.	Single dose	10^5 PFU EEEV-FL93, 70 dpim	
EEEV	Trivalent EILV/EEEV EILV/VEEV EILV/CHIKV	EEEV FL-93, VEEV IAB TC-83, CHIKV 996659	Adult CD-1 mice (age not specified)	10^8 PFU	s.c.	Single dose	10^5 PFU EEEV-FL93, 70 dpim	
VEEV	EILV/EEEV	VEEV IAB TC-83	Adult CD-1 mice (age not specified)	10^8 PFU	s.c.	Single dose	10^3 PFU VEEV-IC 3908, 70 dpim	
VEEV	Trivalent EILV/EEEV, EILV/VEEV EILV/CHIKV	EEEV FL-93, VEEV IAB TC-83, CHIKV 996659	Adult CD-1 mice (age not specified)	10^8 PFU	s.c.	Single dose	10^3 PFU VEEV-IC 3908, 70 dpim	
EEEV (Sindbis virus)	SIN/NAEEEV	EEEV FL93-939	NIH Swiss mice, 8 week old	3.7, 4.7 or 5.7 $\log_{10}$ PFU	s.c.	Single dose	6 $\log_{10}$ PFU FL93-939, 28 dpim	
	SIN/SAEEEV	EEEV BeAr436087	NIH Swiss mice, 8 week old	3.8, 4.8 or 5.8 $\log_{10}$ PFU	s.c.	Single dose	6 $\log_{10}$ PFU FL93-939, 28 dpim	

Vaccine Against Virus	Name	Strain Vaccine Modelled After	Phase	Immunization			Challenge	
				Dose	Route	Schedule	Dose (Strain, Genotype)	F
VEEV	SIN-83	VEEV IAB TC-83	Weanling NIH Swiss mice, 6 day old	10^3, 10^4, 10^5 or 10^6 PFU	s.c.	Single dose	10^6 PFU VEEV IC ZPC738 IC SH3	
			NIH Swiss mice, 6 week old	5×10^5 PFU	s.c.	Two doses	2 x 10^5 or 10^6 PFU VEEV ZPC738, 8 wpim	
	SAAR/TRD	VEEV IAB TrD	NIH Swiss mice, 6 week old	5×10^5 PFU	s.c.	Two doses	2 x 10^5 or 10^6 PFU VEEV ZPC738, 8 wpim	
	SIN/TRD	VEEV IAB TrD	NIH Swiss mice, 6 week old	5×10^5 PFU	s.c.	Two doses	2 x 10^5 or 10^6 PFU VEEV ZPC738, 8 wpim	
	SIN/ZPC	VEEV ID ZPC738	NIH Swiss mice, 6 week old	5×10^5 PFU	s.c.	Two doses	2 x 10^5 or 10^6 PFU VEEV ZPC738, 8 wpim	
	All the above	VEEV IAB TC-83, IAB TrD, ID ZPC738	Syrian golden hamsters, 6 week old	5×10^5 PFU	s.c. in the medial thigh	Single dose	10^6 PFU	
WEEV	SIN/CO92	WEEV CO92-1356	NIH Swiss mice, 6 week old	3.5, 4.5, or 5.0 $\log_{10}$ PFU	s.c. in the medial thigh	Single dose	5.3 $\log_{10}$ PFU WEEV TBT235, 28 dpim	
	SIN/SIN/McM	WEEV McMillan	NIH Swiss mice, 6 week old	4.8 or 5.8 $\log_{10}$ PFU	s.c. in the medial thigh	Single dose	5.0 $\log_{10}$ PFU WEEV McMillan, 28 dpim	
	SIN/EEE/McM	EEEV 436087 and WEEV McMillan	NIH Swiss mice, 6 week old	4.6 or 5.6 $\log_{10}$ PFU	s.c. in the medial thigh	Single dose	5.0 $\log_{10}$ PFU WEEV McMillan, 28 dpim	
	Vaccinia virus-based chimeras							
CHIKV	MVA-CHIKV	LR2006-OPY1	C57BL/6 mice, 6 to 8 week old	10^7 PFU (first dose), 2 × 10^7 PFU (second dose)	i.p.	Two doses (2 weeks apart)	10^6 PFU LR2006-OPY1, 9 wpim	

Vaccine Against Virus	Name	Strain Vaccine Modelled After	Phase	Immunization			Challenge	
				Dose	Route	Schedule	Dose (Strain, Genotype)	F
CHIKV	MVA-CHIK	LR2006-OPY1	BALB/c mice, 4 to 6 week old	10^7 TCID50 units	i.d. injection into the left hind footpad.	Single or two doses (28 days apart)	10^4 LR2006 OPY1 TCID50 units at 39 or 42 dpim	
			AG129, 6 to 10 week old	10^7 TCID50 units	i.d. injection into the left hind footpad.	Single or two doses (28 days apart)	10^2 LR2006 OPY1 TCID50 units at 39 or 42 dpim	
CHIKV	MVA-6KE1, MVA-E3E2, MVA-6KE1E3E2	CHIKV S27	AG129 mice, 7 week old	5×10^6 TCID50	i.m. into the quadriceps muscles of the left leg	Two doses (3 weeks apart)	10^3 TCID50 CHIKV-S27 and CHIKV-IND/NL10, 63 dpim	
EEEV, VEEV, and WEEV	MVA-BN-E/V/W (monovalent) MVA-BN-E + MVA-BN-V + MVA-BN-W (triple mixture of monovalent vaccines) MVA-BN-WEV (trivalent)	WEEV 71 V-1658, EEEV FL93-939NA and VEEV TrD	BALB/c mice, age not specified	10^8 TCID50	s.c. or i.m.	Two doses (28 days apart)	5×10^3 or 10^4 PFU of WEEV Fleming, EEEV PE6, or VEEV TrD, 14 days post booster	
	Adenovirus-based chimeras							
CHIKV	CAdVax-CHIK	LR2006 OPY1	CD-1 or C57BL/6, 6 to 8 week old	10^8 IU	i.p.	Single dose	10^4 CCID50 LR2006 OPY1 or QIMR, 6.5 wpim	

Vaccine Against Virus	Name	Strain Vaccine Modelled After	Phase	Immunization			Challenge	
				Dose	Route	Schedule	Dose (Strain, Genotype)	F
CHIKV	ChAdOx1 Chik	NA	BALB/c, 6 to 8 week old	10^8 IU	i.m.	Single dose	ND	
			AG129, 5 week old	10^8 IU	i.m. in each leg	Single dose	9.7×10^4 PFU LR2006 OPY1, 30 dpim	
	ChAdOx1 Chik ChAdOx1 Chik ΔCap		AG129, 5 week old	10^8 IU	i.m. in each hind leg	Single dose	9.7×10^4 PFU of LR2006 OPY1, 30 dpim	
	CHIK001 (in clinical trials)		Human clinical trial, Phase 1	5×10^9, 2.5×10^{10} or 5×10^{10} vp	i.m.	Single dose	ND	
MAYV	ChAdOx1 May	NA	AG129, 5 week old	1.6×10^4 PFU	i.m. in each leg	Single dose	1.6×10^4 PFU MAYV-CH, 30 dpim	
VEEV	Rad/VEEV#3	VEEV IAB TC-83	BALB/c, 6 to 8 week old	10^7 PFU	i.n.	Three doses (at 0, 7 and 21 days)	Dose ND, 28 dpim	
			BALB/c, 6 to 8 week old	10^7 PFU	i.n.	Two doses (at 0, 21 days)	5000 LD50 TrD, 42 dpim	
WEEV	Ad5-WEEV	WEEV 71V-1658	BALB/c mice, age not specified	10^7 PFU	i.m.	Single or two doses (at 4 weeks)	1.5×10^3 PFU Fleming or 71V-1658, 13 wpim	
WEEV	Ad5-E1	WEEV 71V-1658	BALB/c mice, 6 to 9 week old	10^7 PFU	i.m. in both leg	Single dose	50 LD50 of 71V-1658, 7 dpim, or 400 LD50 CBA87, 1, 3, 5 or 7 dpim	
	Vesiculovirus-based chimeras							
CHIKV	rVSVΔG-CHIKV	CHIKV S27	C57BL/6, 3 week old	10^6 PFU	i.m. into the right hind leg muscle	Single dose	10^4 PFU LR 2006 OPY1, 30 dpim	S

Vaccine Against Virus	Name	Strain Vaccine Modelled After	Phase	Immunization			Challenge	
				Dose	Route	Schedule	Dose (Strain, Genotype)	F
VEEV	rVSIV-VEEV	VEEV ZPC738	CD-1, 4 to 6 week old	10^8/10^7 PFU	i.m.	Single dose	10^4 PFU VEEV ZPC738, 35 or 245 dpim	
VEEV	rISFV-VEEV	VEEV ZPC738	CD-1, 4 to 6 week old	10^8 PFU	i.m.	Single dose	10^4 PFU VEEV ZPC738, 28 dpim	
			CD-1, 4 to 6 week old	10^8 PFU	i.m.	Single dose	10^4 PFU VEEV ZPC738, 35 or 245 dpim	
EEEV	rISFV-EEEV	EEEV FL93-939	CD-1, 4 to 6 week old	10^8 PFU	i.m.	Single dose	10^4 PFU EEEV FL93-939, 28 dpim	
Epitope-based								
CHIKV	E2EP3	NA	C57BL/6 mice, 3 week old	100 µg (50 µg for booster doses)	s.c. in the abdominal flank	Three doses (0, 14 and 21 days)	10^6 PFU CHIKV SGP11, 30 dpim	

[1] s.c., subcutaneous; i.v., intravenous; i.m., intramuscular; i.d., intradermal; i.p., intraperitoneal; i.n., intranasal; i.t./i.s., intrathalamic/ intraspinal; i.pl., intraplantar; i.c., intracranial; dpim, days post immunization; wpim, weeks post immunization; mpim, months post immunization; IRES, internal ribosome entry site; PFU, plaque forming units; TCID50, 50% tissue culture infective dose; CCID50, 50% cell culture infectious dose; IC50, 50% inhibitory concentration; GE, genomic equivalents; IU, infectious units; AID50, 50% animal infectious dose; PRNT50, 50% plaque reduction neutralizing antibody titer; PRNT80, 80% plaque reduction neutralizing antibody titer; PRNT90, 90% plaque reduction neutralizing antibody titer; LD50, median lethal dose; NT50, 50% neutralizing titer; GMT, geometric mean titer; µNT, neutralizing titer; SIN, Sindbis virus; ISFV, Isfahan virus; May, Mayaro virus; EILV, Eilat virus, VSV/VSIV, vesicular stomatitis virus; MV, measles virus; MVA, modified vaccinia virus Ankara; NP, not provided; NA, not applicable; WT, wild type. Data curated from literature reported through February 2021.

References

1. Atkins, G.J. The Pathogenesis of Alphaviruses. ISRN Virol. 2013, 2013, 22.
2. Zaid, A.; Burt, F.J.; Liu, X.; Poo, Y.S.; Zandi, K.; Suhrbier, A.; Weaver, S.; Texeira, M.; Mahalingam, S. Arthritogenic alph aviruses: Epidemiological and clinical perspective on emerging arboviruses. Lancet Infect. Dis. 2020.
3. Suhrbier, A.; Jaffar-Bandjee, M.C.; Gasque, P. Arthritogenic alphaviruses—An overview. Nat. Rev. Rheumatol. 2012, 8, 420–429.
4. Zacks, M.A.; Paessler, S. Encephalitic alphaviruses. Vet. Microbiol. 2010, 140, 281–286.
5. Wahid, B.; Ali, A.; Rafique, S.; Idrees, M. Global expansion of chikungunya virus: Mapping the 64-year history. Int. J. Inf ect. Dis. 2017, 58, 69–76.
6. Haddow, A.; Davies, C.W.; Walker, A.J. O'nyong-nyong fever: An epidemic virus disease in East Africa 1. Introduction. T rans. R. Soc. Trop. Med. Hyg. 1960, 54, 517–522.

7. Bessaud, M.; Peyrefitte, C.N.; Pastorino, B.A.; Tock, F.; Merle, O.; Colpart, J.J.; Dehecq, J.S.; Girod, R.; Jaffar-Bandje e, M.C.; Glass, P. J.; et al. Chikungunya virus strains, Reunion Island outbreak. Emerg. Infect. Dis. 2006, 12, 1604–160 6.
8. Aaskov, J.G.; Mataika, J.U.; Lawrence, G.W.; Rabukawaqa, V.; Tucker, M.M.; Miles, J.A.; Dalglish, D.A. An epidemic of Ross River virus infection in Fiji, 1979. Am. J. Trop. Med. Hyg. 1981, 30, 1053–1059.
9. Tsetsarkin, K.A.; Vanlandingham, D.L.; McGee, C.E.; Higgs, S. A single mutation in chikungunya virus affects vector sp ecificity and epidemic potential. PLoS Pathog. 2007, 3, e201.
10. Tsetsarkin, K.A.; McGee, C.E.; Volk, S.M.; Vanlandingham, D.L.; Weaver, S.C.; Higgs, S. Epistatic roles of E2 glycoprot ein mutations in adaption of chikungunya virus to Aedes albopictus and Ae. aegypti mosquitoes. PLoS ONE 2009, 4, e 6835.
11. Rezza, G.; Chen, R.; Weaver, S.C. O'nyong-nyong fever: A neglected mosquito-borne viral disease. Pathog. Glob. Heal th 2017, 111, 271–275.
12. Acosta-Ampudia, Y.; Monsalve, D.M.; Rodriguez, Y.; Pacheco, Y.; Anaya, J.M.; Ramirez-Santana, C. Mayaro: An emerg ing viral threat? Emerg. Microbe. Infect. 2018, 7, 163.
13. Ganjian, N.; Riviere-Cinnamond, A. Mayaro virus in Latin America and the Caribbean. Rev. Panam. Salud. Publica 202 0, 44, 14.
14. Pezzi, L.; LaBeaud, A.D.; Reusken, C.B.; Drexler, J.F.; Vasilakis, N.; Diallo, M.; Simon, F.; Jaenisch, T.; Gallian, P.; Sall, A.; et al. GloPID-R report on chikungunya, o'nyong-nyong and Mayaro virus, part 2: Epidemiological distribution of o'ny ong-nyong virus. Antivir. Res. 2019, 172, 104611.
15. Pezzi, L.; Rodriguez-Morales, A.J.; Reusken, C.B.; Ribeiro, G.S.; LaBeaud, A.D.; Lourenço-de-Oliveira, R.; Brasil, P.; L ecuit, M.; Failloux, A.B.; Gallian, P.; et al. GloPID-R report on chikungunya, o'nyong-nyong and Mayaro virus, part 3: Ep idemiological distribution of Mayaro virus. Antivir. Res. 2019, 172, 104610.
16. Pezzi, L.; Reusken, C.B.; Weaver, S.C.; Drexler, J.F.; Busch, M.; LaBeaud, A.D.; Diamond, M. S.; Vasilakis, N.; Drebot, M. A.; Siqueira, A.M.; et al. GloPID-R report on Chikungunya, O'nyong-nyong and Mayaro virus, part I: Biological diagn ostics. Antivir. Res. 2019, 166, 66–81.
17. Seyler, T.; Hutin, Y.; Ramanchandran, V.; Ramakrishnan, R.; Manickam, P.; Murhekar, M. Estimating the burden of dise ase and the economic cost attributable to chikungunya, Andhra Pradesh, India, 2005–2006. Trans. R. Soc. Trop. Med. Hyg. 2010, 104, 133–138.
18. Alvis-Zakzuk, N.J.; Diaz-Jimenez, D.; Castillo-Rodriguez, L.; Castaneda-Orjuela, C.; Paternina-Caicedo, A.; Pinzon-Re dondo, H.; Carrasquilla-Sotomayor, M.; Alvis-Guzmán, N.; De La Hoz-Restrepo, F. Economic Costs of Chikungunya Vir us in Colombia. Value Health Reg. Issues 2018, 17, 32–37.
19. Thompson, R.; del Martin Campo, J.; Constenla, D. A review of the economic evidence of Aedes-borne arboviruses and Aedes-borne arboviral disease prevention and control strategies. Expert Rev. Vaccin. 2020, 19, 143–162.
20. Cunha, R.V.D.; Trinta, K.S. Chikungunya virus: Clinical aspects and treatment—A Review. Mem. Inst. Oswaldo Cruz 20 17, 112, 523–531.
21. Lundstrom, K. Alphavirus-based vaccines. Viruses 2014, 6, 2392–2415.
22. Panning, M.; Grywna, K.; van Esbroeck, M.; Emmerich, P.; Drosten, C. Chikungunya fever in travelers returning to Euro pe from the Indian Ocean region, 2006. Emerg. Infect. Dis. 2008, 14, 416–422.
23. Kam, Y.W.; Lum, F.M.; Teo, T.H.; Lee, W.W.; Simarmata, D.; Harjanto, S.; Chua, C.L.; Chan, Y.F.; Wee, J.K.; Chow, A.; et al. Early neutralizing IgG response to Chikungunya virus in infected patients targets a dominant linear epitope on the E2 glycoprotein. EMBO Mol. Med. 2012, 4, 330–343.
24. Pierro, A.; Rossini, G.; Gaibani, P.; Finarelli, A.C.; Moro, M.L.; Landini, M.P.; Sambri, V. Persistence of anti-chikungunya virus-specific antibodies in a cohort of patients followed from the acute phase of infection after the 2007 outbreak in Ital y. New Microbe. New Infect. 2015, 7, 23–25.
25. Chua, C.L.; Sam, I.C.; Chiam, C.W.; Chan, Y.F. The neutralizing role of IgM during early Chikungunya virus infection. P LoS ONE 2017, 12, e0171989.
26. Borgherini, G.; Poubeau, P.; Staikowsky, F.; Lory, M.; Le Moullec, N.; Becquart, J.P.; Wengling, C.; Michault, A.; Pagani n, F. Outbreak of chikungunya on Reunion Island: Early clinical and laboratory features in 157 adult patients. Clin. Infec t. Dis. 2007, 44, 1401–1407.
27. Malvy, D.; Ezzedine, K.; Mamani-Matsuda, M.; Autran, B.; Tolou, H.; Receveur, M-C.; Pistone, T.; Rambert, J.; Moynet, D.; Mossalayi, D. Destructive arthritis in a patient with chikungunya virus infection with persistent specific IgM antibodie s. BMC Infect. Dis. 2009, 9, 200.
28. Bozza, F.A.; Moreira-Soto, A.; Rockstroh, A.; Fischer, C.; Nascimento, A.D.; Calheiros, A.S.; Drosten, C.; Bozza, P.T.; S ouza, T.; Ulbert, S.; et al. Differential Shedding and Antibody Kinetics of Zika and Chikungunya Viruses, Brazil. Emerg. I nfect. Dis. 2019, 25, 311–315.
29. Nitatpattana, N.; Kanjanopas, K.; Yoksan, S.; Satimai, W.; Vongba, N.; Langdatsuwan, S.; Nakgoi, K.; Ratchakum, S.; Wauquier, N.; Souris, M.; et al. Long-term persistence of Chikungunya virus neutralizing antibodies in human populatio ns of North Eastern Thailand. Virol. J. 2014, 11, 183.

30. Shore, H. O’nyong-nyong fever: An epidemic virus disease in East Africa: III Some clinical and epidemiological observations in the Northern Province of Uganda. Trans. R. Soc. Trop. Med. Hyg. 1961, 55, 361–373.
31. Williams, M.C.; Woodall, J.P.; Corbet, P.S.; Gillett, J.D. O’nyong-Nyong Fever: An Epidemic Virus Disease in East Africa. 8. Virus Isolations from Anopheles Mosquitoes. Trans. R. Soc. Trop. Med. Hyg. 1965, 59, 300–306.
32. Kiwanuka, N.; Sanders, E.J.; Rwaguma, E.B.; Kawamata, J.; Ssengooba, F.P.; Najjemba, R.; Were, W.A.; Lamunu, M.; Bagambisa, G.; Burkot, T.R.; et al. O’nyong-nyong fever in south-central Uganda, 1996–1997: Clinical features and validation of a clinical case definition for surveillance purposes. Clin. Infect. Dis. 1999, 29, 1243–1250.
33. Tappe, D.; Kapaun, A.; Emmerich, P.; de Mendonca Campos, R.; Cadar, D.; Gunther, S.; Schmidt-Chanasit, J. O’nyong-nyong virus infection imported to Europe from Kenya by a traveler. Emerg. Infect. Dis. 2014, 20, 1766–1767.
34. Bessaud, M.; Peyrefitte, C.N.; Pastorino, B.A.; Gravier, P.; Tock, F.; Boete, F.; Tolou, H.J.; Grandadam, M. O’nyong-nyong Virus, Chad. Emerg. Infect. Dis. 2006, 12, 1248–1250.
35. Diagne, C.T.; Bengue, M.; Choumet, V.; Hamel, R.; Pompon, J.; Misse, D. Mayaro Virus Pathogenesis and Transmission Mechanisms. Pathogens 2020, 9, 738.
36. Mourao, M.P.; Bastos, M.D.S.; de Figueiredo, R.P.; Gimaque, J.B.; Galusso Edos, S.; Kramer, V.M.; de Oliveira, C.M.; Naveca, F.G.; Figueiredo, L.T. Mayaro fever in the city of Manaus, Brazil, 2007–2008. Vector Borne Zoonotic Dis. 2012, 12, 42–46.
37. Halsey, E.S.; Siles, C.; Guevara, C.; Vilcarromero, S.; Jhonston, E.J.; Ramal, C.; Aguilar, P.V.; Ampuero, J.S. Mayaro virus infection, Amazon Basin region, Peru, 2010–2013. Emerg. Infect. Dis. 2013, 19, 1839–1842.
38. Figueiredo, L.T.; Nogueira, R.M.; Cavalcanti, S.M.; Schatzmayr, H.; da Rosa, A.T. Study of two different enzyme immunoassays for the detection of Mayaro virus antibodies. Mem. Inst. Oswaldo Cruz 1989, 84, 303–307.
39. Santiago, F.W.; Halsey, E.S.; Siles, C.; Vilcarromero, S.; Guevara, C.; Silvas, J.A.; Ramal, C.; Ampuero, J.S.; Aguilar, P.V. Long-Term Arthralgia after Mayaro Virus Infection Correlates with Sustained Pro-inflammatory Cytokine Response. PLoS Negl. Trop. Dis. 2015, 9, e0004104.
40. Harley, D.; Sleigh, A.; Ritchie, S. Ross River virus transmission, infection, and disease: A cross-disciplinary review. Clin. Microbiol. Rev. 2001, 14, 909–932.
41. Farmer, J.F.; Suhrbier, A. Interpreting paired serology for Ross River virus and Barmah Forest virus diseases. Aust. J. Gen. Pract. 2019, 48, 645–649.
42. Barton, A.J.; Bielefeldt-Ohmann, H. Clinical Presentation, Progression, and Management of Five Cases of Ross River Virus Infection in Performance Horses Located in Southeast Queensland: A Longitudinal Case Series. J. Equin. Vet. Sci. 2017, 51, 34–40.
43. Azuolas, J.K.; Wishart, E.; Bibby, S.; Ainsworth, C. Isolation of Ross River virus from mosquitoes and from horses with signs of musculo-skeletal disease. Aust. Vet. J. 2003, 81, 344–347.
44. Kapeleris, J.; Lowe, P.; Phillips, D.; Wyatt, D.; Batham, M.; Devine, P. IgG avidity in the diagnosis of acute Ross River virus infection. Dis. Marker. 1996, 12, 279–282.
45. Calisher, C.H.; Meurman, O.; Brummer-Korvenkontio, M.; Halonen, P.E.; Muth, D.J. Sensitive enzyme immunoassay for detecting immunoglobulin M antibodies to Sindbis virus and further evidence that Pogosta disease is caused by a western equine encephalitis complex virus. J. Clin. Microbiol. 1985, 22, 566–571.
46. Kurkela, S.; Manni, T.; Myllynen, J.; Vaheri, A.; Vapalahti, O. Clinical and laboratory manifestations of Sindbis virus infection: Prospective study, Finland, 2002–2003. J. Infect. Dis. 2005, 191, 1820–1829.
47. Niklasson, B.; Espmark, A.; Lundstrom, J. Occurrence of arthralgia and specific IgM antibodies three to four years after Ockelbo disease. J. Infect. Dis. 1988, 157, 832–835.
48. Griffin, D.E. Neurotropic Alphaviruses. In Neurotropic Viral Infections, 2nd ed.; Reis, C.S., Ed.; Springer International Publishing: Cham, Switzerland, 2016; pp. 175–204.
49. Calisher, C.H.; Berardi, V.P.; Muth, D.J.; Buff, E.E. Specificity of immunoglobulin M and G antibody responses in humans infected with eastern and western equine encephalitis viruses: Application to rapid serodiagnosis. J. Clin. Microbiol. 1986, 23, 369–372.
50. Gardner, J.; Anraku, I.; Le, T.T.; Larcher, T.; Major, L.; Roques, P.; Schroder, W.A.; Higgs, S.; Suhrbier, A. Chikungunya virus arthritis in adult wild-type mice. J. Virol. 2010, 84, 8021–8032.
51. Poo, Y.S.; Rudd, P.A.; Gardner, J.; Wilson, J.A.; Larcher, T.; Colle, M.A.; Le, T.T.; Nakaya, H.I.; Warrilow, D.; Allcock, R.; et al. Multiple immune factors are involved in controlling acute and chronic chikungunya virus infection. PLoS Negl. Trop. Dis. 2014, 8, e3354.
52. Hawman, D.W.; Stoermer, K.A.; Montgomery, S.A.; Pal, P.; Oko, L.; Diamond, M.S.; Morrison, T.E. Chronic joint disease caused by persistent Chikungunya virus infection is controlled by the adaptive immune response. J. Virol. 2013, 87, 13878–13888.
53. Johnson, R.T. Virus Invasion of the Central Nervous System: A Study of Sindbis Virus Infection in the Mouse Using Fluorescent Antibody. Am. J. Pathol. 1965, 46, 929–943.

54. Burdeinick-Kerr, R.; Wind, J.; Griffin, D.E. Synergistic roles of antibody and interferon in noncytolytic clearance of Sindb is virus from different regions of the central nervous system. J. Virol. 2007, 81, 5628–5636.

55. Nilaratanakul, V.; Chen, J.; Tran, O.; Baxter, V.K.; Troisi, E.M.; Yeh, J.X.; Griffin, D.E. Germ Line IgM Is Sufficient, but N ot Required, for Antibody-Mediated Alphavirus Clearance from the Central Nervous System. J. Virol. 2018, 92, e02081-17.

56. Fragkoudis, R.; Ballany, C.M.; Boyd, A.; Fazakerley, J.K. In Semliki Forest virus encephalitis, antibody rapidly clears inf ectious virus and is required to eliminate viral material from the brain, but is not required to generate lesions of demyeli nation. J. Gen. Virol. 2008, 89, 2565–2568.

57. Amor, S.; Scallan, M.F.; Morris, M.M.; Dyson, H.; Fazakerley, J.K. Role of immune responses in protection and pathoge nesis during Semliki Forest virus encephalitis. J. Gen. Virol. 1996, 77, 281–291.

58. Fazakerley, J.K.; Webb, H.E. Semliki Forest virus-induced, immune-mediated demyelination: Adoptive transfer studies and viral persistence in nude mice. J. Gen. Virol. 1987, 68, 377–385.

59. Metcalf, T.U.; Baxter, V.K.; Nilaratanakul, V.; Griffin, D.E. Recruitment and retention of B cells in the central nervous sys tem in response to alphavirus encephalomyelitis. J. Virol. 2013, 87, 2420–2429.

60. Metcalf, T.U.; Griffin, D.E. Alphavirus-induced encephalomyelitis: Antibody-secreting cells and viral clearance from the n ervous system. J. Virol. 2011, 85, 11490–11501.

61. Teo, T.H.; Lum, F.M.; Claser, C.; Lulla, V.; Lulla, A.; Merits, A.; Renia, L.; Ng, L. F. A pathogenic role for CD4+ T cells dur ing Chikungunya virus infection in mice. J. Immunol. 2013, 190, 259–269.

62. Lum, F.M.; Teo, T.H.; Lee, W.W.; Kam, Y.W.; Renia, L.; Ng, L.F. An essential role of antibodies in the control of Chikung unya virus infection. J. Immunol. 2013, 190, 6295–6302.

63. Olitsky, P.K.; Cox, H.R. Active Immunication of Guinea Pigs with the Virus of Equine Encephalomyelitis: I. Quantitative Experiments with Various Preparations of Active Virus. J. Exp. Med. 1936, 63, 311–324.

64. Cox, H.R.; Olitsky, P.K. Active Immunization of Guinea Pigs with the Virus of Equine Encephalomyelitis: Iii. Quantitative Studies of Serum Antiviral Bodies in Animals Immunized with Active and Inactive Virus. J. Exp. Med. 1936, 64, 217–22 2.

65. Cox, H.R.; Olitsky, P.K. Active Immunization of Guinea Pigs with the Virus of Equine Encephalomyelitis: Iv. Effect of Im mune Serum on Antigenicity of Active and Inactive Virus. J. Exp. Med. 1936, 64, 223–232.

66. Olitsky, P.K.; Harford, C.G. Intraperitoneal and Intracerebral Routes in Serum Protection Tests with the Virus of Equine Encephalomyelitis: Iii. Comparison of Antiviral Serum Constituents from Guinea Pigs Immunized with Active or Formoliz ed Inactive Virus. J. Exp. Med. 1938, 68, 779–787.

67. Morgan, I.M.; Schlesinger, R.W.; Olitsky, P.K. Induced Resistance of the Central Nervous System to Experimental Infec tion with Equine Encephalomyelitis Virus: I. Neutralizing Antibody in the Central Nervous System in Relation to Cerebra l Resistance. J. Exp. Med. 1942, 76, 357–369.

68. Griffin, D.E.; Johnson, R.T. Role of the immune response in recovery from Sindbis virus encephalitis in mice. J. Immun ol. 1977, 118, 1070–1075.

69. Kimura, T.; Griffin, D.E. Extensive immune-mediated hippocampal damage in mice surviving infection with neuroadapte d Sindbis virus. Virology 2003, 311, 28–39.

70. Rabinowitz, S.G.; Adler, W.H. Host defenses during primary Venezuelan equine encephalomyelitis virus infection in mic e. I. Passive transfer of protection with immune serum and immune cells. J. Immunol. 1973, 110, 1345–1353.

71. Couderc, T.; Khandoudi, N.; Grandadam, M.; Visse, C.; Gangneux, N.; Bagot, S.; Prost, J. F.; Lecuit, M. Prophylaxis an d therapy for Chikungunya virus infection. J. Infect. Dis. 2009, 200, 516–523.

72. Lee, C.Y.; Kam, Y.W.; Fric, J.; Malleret, B.; Koh, E.G.; Prakash, C.; Huang, W.; Lee, W. W.; Lin, C.; Lin, R. T. Chikungun ya virus neutralization antigens and direct cell-to-cell transmission are revealed by human antibody-escape mutants. P LoS Pathog. 2011, 7, e1002390.

73. Holzer, G.W.; Coulibaly, S.; Aichinger, G.; Savidis-Dacho, H.; Mayrhofer, J.; Brunner, S.; Schmid, K.; Kistner, O.; Aasko v, J. G.; Falkner, F.G.; et al. Evaluation of an inactivated Ross River virus vaccine in active and passive mouse immuniz ation models and establishment of a correlate of protection. Vaccine 2011, 29, 4132–4141.

74. Kraaijeveld, C.A.; Benaissa-Trouw, B.J.; Harmsen, M.; Snippe, H. Adoptive transfer of immunity against virulent Semliki Forest virus with immune spleen cells from mice infected with avirulent Semliki Forest virus. Arch. Virol. 1986, 91, 83–9 2.

75. Jose, J.; Snyder, J.E.; Kuhn, R.J. A structural and functional perspective of alphavirus replication and assembly. Future Microbiol. 2009, 4, 837–856.

76. Stec, D.S.; Waddell, A.; Schmaljohn, C.S.; Cole, G.A.; Schmaljohn, A.L. Antibody-selected variation and reversion in Si ndbis virus neutralization epitopes. J. Virol. 1986, 57, 715–720.

77. Boere, W.A.; Harmsen, T.; Vinje, J.; Benaissa-Trouw, B.J.; Kraaijeveld, C.A.; Snippe, H. Identification of distinct antigeni c determinants on Semliki Forest virus by using monoclonal antibodies with different antiviral activities. J. Virol. 1984, 5 2, 575–582.

78. Roehrig, J.T.; Mathews, J.H. The neutralization site on the E2 glycoprotein of Venezuelan equine encephalomyelitis (TC-83) virus is composed of multiple conformationally stable epitopes. Virology 1985, 142, 347–356.

79. Vrati, S.; Fernon, C.A.; Dalgarno, L.; Weir, R.C. Location of a major antigenic site involved in Ross River virus neutralization. Virology 1988, 162, 346–353.

80. Navaratnarajah, C.K.; Kuhn, R.J. Functional characterization of the Sindbis virus E2 glycoprotein by transposon linker-insertion mutagenesis. Virology 2007, 363, 134–147.

81. Hunt, A.R.; Frederickson, S.; Maruyama, T.; Roehrig, J.T.; Blair, C.D. The first human epitope map of the alphaviral E1 and E2 proteins reveals a new E2 epitope with significant virus neutralizing activity. PLoS Negl. Trop. Dis. 2010, 4, e739.

82. Kam, Y.W.; Lee, W.W.; Simarmata, D.; Le Grand, R.; Tolou, H.; Merits, A.; Roques, P.; Ng, L. F. Unique epitopes recognized by antibodies induced in Chikungunya virus-infected non-human primates: Implications for the study of immunopathology and vaccine development. PLoS ONE 2014, 9, e95647.

83. Adouchief, S.; Smura, T.; Vapalahti, O.; Hepojoki, J. Mapping of human B-cell epitopes of Sindbis virus. J. Gen. Virol. 2016, 97, 2243–2254.

84. Chanas, A.C.; Gould, E.A.; Clegg, J.C.; Varma, M.G. Monoclonal antibodies to Sindbis virus glycoprotein E1 can neutralize, enhance infectivity, and independently inhibit haemagglutination or haemolysis. J. Gen. Virol. 1982, 58, 37–46.

85. Despres, P.; Griffin, J.W.; Griffin, D.E. Antiviral activity of alpha interferon in Sindbis virus-infected cells is restored by anti-E2 monoclonal antibody treatment. J. Virol. 1995, 69, 7345–7348.

86. Despres, P.; Griffin, J.W.; Griffin, D.E. Effects of anti-E2 monoclonal antibody on sindbis virus replication in AT3 cells expressing bcl-2. J. Virol. 1995, 69, 7006–7014.

87. Mendoza, Q.P.; Stanley, J.; Griffin, D.E. Monoclonal antibodies to the E1 and E2 glycoproteins of Sindbis virus: Definition of epitopes and efficiency of protection from fatal encephalitis. J. Gen. Virol. 1988, 69, 3015–3022.

88. Stanley, J.; Cooper, S.J.; Griffin, D.E. Monoclonal antibody cure and prophylaxis of lethal Sindbis virus encephalitis in mice. J. Virol. 1986, 58, 107–115.

89. Boere, W.A.; Benaissa-Trouw, B.J.; Harmsen, T.; Erich, T.; Kraaijeveld, C.A.; Snippe, H. Mechanisms of monoclonal antibody-mediated protection against virulent Semliki Forest virus. J. Virol. 1985, 54, 546–551.

90. Smith, S.A.; Silva, L.A.; Fox, J.M.; Flyak, A.I.; Kose, N.; Sapparapu, G.; Khomandiak, S.; Ashbrook, A. W.; Kahle, K. M.; Fong, R. H; et al. Isolation and Characterization of Broad and Ultrapotent Human Monoclonal Antibodies with Therapeutic Activity against Chikungunya Virus. Cell Host Microbe 2015, 18, 86–95.

91. Chua, C.L.; Chan, Y.F.; Sam, I.C. Characterisation of mouse monoclonal antibodies targeting linear epitopes on Chikungunya virus E2 glycoprotein. J. Virol. Method. 2014, 195, 126–133.

92. Pal, P.; Dowd, K.A.; Brien, J.D.; Edeling, M.A.; Gorlatov, S.; Johnson, S.; Lee, I.; Akahata, W.; Nabel, G. J.; Richter, M. K.; et al. Development of a highly protective combination monoclonal antibody therapy against Chikungunya virus. PLoS Pathog. 2013, 9, e1003312.

93. Goh, L.Y.; Hobson-Peters, J.; Prow, N.A.; Baker, K.; Piyasena, T.B.; Taylor, C.T.; Rana, A.; Hastie, M. L.; Gorman, J. J.; Hall, R. A. The Chikungunya Virus Capsid Protein Contains Linear B Cell Epitopes in the N- and C-Terminal Regions that are Dependent on an Intact C-Terminus for Antibody Recognition. Viruses 2015, 7, 2943–2964.

94. Goh, L.Y.H.; Hobson-Peters, J.; Prow, N.A.; Gardner, J.; Bielefeldt-Ohmann, H.; Suhrbier, A.; Hall, R. A. Monoclonal antibodies specific for the capsid protein of chikungunya virus suitable for multiple applications. J. Gen. Virol. 2015, 96, 507–512.

95. Sun, S.; Xiang, Y.; Akahata, W.; Holdaway, H.; Pal, P.; Zhang, X.; Diamond, M. S.; Nabel, G. J.; Rossmann, M. G. Structural analyses at pseudo atomic resolution of Chikungunya virus and antibodies show mechanisms of neutralization. eLife 2013, 2, e00435.

96. Voss, J.E.; Vaney, M.C.; Duquerroy, S.; Vonrhein, C.; Girard-Blanc, C.; Crublet, E.; Thompson, A.; Bricogne, G.; Rey, F. A. Glycoprotein organization of Chikungunya virus particles revealed by X-ray crystallography. Nature 2010, 468, 709–712.

97. Broeckel, R.; Fox, J.M.; Haese, N.; Kreklywich, C.N.; Sukulpovi-Petty, S.; Legasse, A.; Smith, P. P.; Denton, M.; Corvey, C.; Krishnan, S.; et al. Therapeutic administration of a recombinant human monoclonal antibody reduces the severity of chikungunya virus disease in rhesus macaques. PLoS Negl. Trop. Dis. 2017, 11, e0005637.

98. Fox, J.M.; Long, F.; Edeling, M.A.; Lin, H.; van Duijl-Richter, M.K.S.; Fong, R.H.; Kahle, K. M.; Smit, J. M.; Jin, J.; Simmons, G.; et al. Broadly Neutralizing Alphavirus Antibodies Bind an Epitope on E2 and Inhibit Entry and Egress. Cell 2015, 163, 1095–1107.

99. Kim, A.S.; Austin, S.K.; Gardner, C.L.; Zuiani, A.; Reed, D.S.; Trobaugh, D.W.; Sun, C.; Basore, K.; Williamson, L. E.; Crowe, J. E; et al. Protective antibodies against Eastern equine encephalitis virus bind to epitopes in domains A and B of the E2 glycoprotein. Nat. Microbiol. 2019, 4, 187–197.

100. Zhao, J.; Sun, E.C.; Liu, N.H.; Yang, T.; Xu, Q.Y.; Qin, Y.L.; Yang, Y. H.; Wu, D. L. Phage display identifies an Eastern equine encephalitis virus glycoprotein E2-specific B cell epitope. Vet. Immunol. Immunopathol. 2012, 148, 364–368.

101. Sun, E.C.; Zhao, J.; Yang, T.; Xu, Q.Y.; Qin, Y.L.; Wang, W.S.; Wei, P.; Sun, L.; Sun, J.; Wu, D.L. Analysis of murine B-cell epitopes on Eastern equine encephalitis virus glycoprotein E2. Appl. Microbiol. Biotechnol. 2013, 97, 6359–6372.

102. Powell, L.A.; Fox, J.M.; Kose, N.; Kim, A.S.; Majedi, M.; Bombardi, R.; Carnahan, R. H.; Slaughter, J. C.; Morrison, T. E.; Diamond, M.; et al. Human monoclonal antibodies against Ross River virus target epitopes within the E2 protein and protect against disease. PLoS Pathog. 2020, 16, e1008517.

103. Earnest, J.T.; Basore, K.; Roy, V.; Bailey, A.L.; Wang, D.; Alter, G.; Fremont, D. H.; Diamond, M. S. Neutralizing antibodies against Mayaro virus require Fc effector functions for protective activity. J. Exp. Med. 2019, 216, 2282–2301.

104. Zhang, R.; Kim, A.S.; Fox, J.M.; Nair, S.; Basore, K.; Klimstra, W.B.; Rimkunas, R.; Fong, R. H.; Lin, H.; Poddar, S.; et al. Mxra8 is a receptor for multiple arthritogenic alphaviruses. Nature 2018, 557, 570–574.

105. Zhang, R.; Earnest, J.T.; Kim, A.S.; Winkler, E.S.; Desai, P.; Adams, L.J.; Hu, G.; Bullock, C.; Gold, B.; Cherry, S.; et al. Expression of the Mxra8 Receptor Promotes Alphavirus Infection and Pathogenesis in Mice and Drosophila. Cell Rep. 2019, 28, 2647–2658.e5.

106. Basore, K.; Kim, A.S.; Nelson, C.A.; Zhang, R.; Smith, B.K.; Uranga, C.; Vang, L.; Cheng, M.; Gross, M. L.; Smith, J.; et al. Cryo-EM Structure of Chikungunya Virus in Complex with the Mxra8 Receptor. Cell 2019, 177, 1725–1737.e16.

107. Song, H.; Zhao, Z.; Chai, Y.; Jin, X.; Li, C.; Yuan, F.; Liu, S.; Gao, Z.; Wang, H.; Song, J.; et al. Molecular Basis of Arthritogenic Alphavirus Receptor MXRA8 Binding to Chikungunya Virus Envelope Protein. Cell 2019, 177, 1714–1724.e12.

108. Gould, E.; Pettersson, J.; Higgs, S.; Charrel, R.; de Lamballerie, X. Emerging arboviruses: Why today? One Health 2017, 4, 1–13.

109. Weaver, S.C. Urbanization and geographic expansion of zoonotic arboviral diseases: Mechanisms and potential strategies for prevention. Trends Microbiol. 2013, 21, 360–363.

110. Zahouli, J.B.Z.; Koudou, B.G.; Muller, P.; Malone, D.; Tano, Y.; Utzinger, J. Urbanization is a main driver for the larval ecology of Aedes mosquitoes in arbovirus-endemic settings in south-eastern Cote d'Ivoire. PLoS Negl. Trop. Dis. 2017, 11, e0005751.

111. Kilpatrick, A.M.; Randolph, S.E. Drivers, dynamics, and control of emerging vector-borne zoonotic diseases. Lancet 2012, 380, 1946–1955.

112. Vazeille, M.; Moutailler, S.; Pages, F.; Jarjaval, F.; Failloux, A.B. Introduction of Aedes albopictus in Gabon: What consequences for dengue and chikungunya transmission? Trop. Med. Int. Health 2008, 13, 1176–1179.

113. Naish, S.; Hu, W.; Mengersen, K.; Tong, S. Spatio-temporal patterns of Barmah Forest virus disease in Queensland, Australia. PLoS ONE 2011, 6, e25688.

114. Reed, D.S.; Glass, P.J.; Bakken, R.R.; Barth, J.F.; Lind, C.M.; da Silva, L.; Hart, M.K.; Rayner, J.; Alterson, K.; Custer, M.; et al. Combined alphavirus replicon particle vaccine induces durable and cross-protective immune responses against equine encephalitis viruses. J. Virol. 2014, 88, 12077–12086.

115. Wressnigg, N.; van der Velden, M.V.; Portsmouth, D.; Draxler, W.; O'Rourke, M.; Richmond, P.; Hall, S.; McBride, W.J. H.; Redfern, A.; Aaskvo, J.; et al. An inactivated Ross River virus vaccine is well tolerated and immunogenic in an adult population in a randomized phase 3 trial. Clin. Vaccine Immunol. 2015, 22, 267–273.

116. Chang, L.J.; Dowd, K.A.; Mendoza, F.H.; Saunders, J.G.; Sitar, S.; Plummer, S.H.; Yamshchikov, G.; Sarwar, U.N.; Hu, Z.; Enama, M.E.; et al. Safety and tolerability of chikungunya virus-like particle vaccine in healthy adults: A phase 1 dose-escalation trial. Lancet 2014, 384, 2046–2052.

117. Chen, G.L.; Coates, E.E.; Plummer, S.H.; Carter, C.A.; Berkowitz, N.; Conan-Cibotti, M.; Cox, J.H.; Beck, A.; O'Callahan, M.; Andrews, C.; et al. Effect of a Chikungunya Virus-Like Particle Vaccine on Safety and Tolerability Outcomes: A Randomized Clinical Trial. JAMA 2020, 323, 1369–1377.

118. Akahata, W.; Nabel, G.J. A specific domain of the Chikungunya virus E2 protein regulates particle formation in human cells: Implications for alphavirus vaccine design. J. Virol. 2012, 86, 8879–8883.

119. Chen, R.; Puri, V.; Fedorova, N.; Lin, D.; Hari, K.L.; Jain, R.; Rodas, J.D.; Das, S.R.; Shabman, R.S.; Weaver, S.C. Comprehensive Genome Scale Phylogenetic Study Provides New Insights on the Global Expansion of Chikungunya Virus. J. Virol. 2016, 90, 10600–10611.

120. Xavier, J.; Fonseca, V.; Bezerra, J.F.; do Monte Alves, M.; Mares-Guia, M.A.; Claro, I.M.; de Jesus, R.; Adelino, T.; Araújo, E.; Cavalcante, K.R.L.J; et al. Chikungunya virus ECSA lineage reintroduction in the northeasternmost region of Brazil. Int. J. Infect. Dis. 2021, 105, 120–123.

121. Phadungsombat, J.; Imad, H.; Rahman, M.; Nakayama, E.E.; Kludkleeb, S.; Ponam, T.; Rahim, R.; Hasan, A.; Poltep, K.; Yamanaka, A.; et al. A Novel Sub-Lineage of Chikungunya Virus East/Central/South African Genotype Indian Ocean Lineage Caused Sequential Outbreaks in Bangladesh and Thailand. Viruses 2020, 12, 1319.

122. Fabri, A.A.; Rodrigues, C.; Santos, C.C.D.; Chalhoub, F.L.L.; Sampaio, S.A.; Faria, N.; Torres, M.C.; Fonseca, V.; Brasil, P.; Calvet, G.; et al. Co-Circulation of Two Independent Clades and Persistence of CHIKV-ECSA Genotype during Epidemic Waves in Rio de Janeiro, Southeast Brazil. Pathogens 2020, 9, 984.

123. Harsha, P.K.; Reddy, V.; Rao, D.; Pattabiraman, C.; Mani, R.S. Continual circulation of ECSA genotype and identification of a novel mutation I317V in the E1 gene of Chikungunya viral strains in southern India during 2015–2016. J. Med. Virol. 2020, 92, 1007–1012.

124. Akahata, W.; Yang, Z.Y.; Andersen, H.; Sun, S.; Holdaway, H.A.; Kong, W.P; Lewis, M.G.; Higgs, S.; Rossmann, M.G.; Rao, S.; et al. A virus-like particle vaccine for epidemic Chikungunya virus protects nonhuman primates against infectio n. Nat. Med. 2010, 16, 334–338.

125. Erasmus, J.H.; Seymour, R.L.; Kaelber, J.T.; Kim, D.Y.; Leal, G.; Sherman, M.B.; Frolov, I.; Chiu, W.; Weaver, S.C.; Nas ar, F. Novel Insect-Specific Eilat Virus-Based Chimeric Vaccine Candidates Provide Durable, Mono- and Multivalent, Si ngle-Dose Protection against Lethal Alphavirus Challenge. J. Virol. 2018, 92, e01274-17.

126. Abeyratne, E.; Tharmarajah, K.; Freitas, J.R.; Mostafavi, H.; Mahalingam, S.; Zaid, A.; Zaman, M.; Taylor, A. Liposomal Delivery of the RNA Genome of a Live-Attenuated Chikungunya Virus Vaccine Candidate Provides Local, but Not Syste mic Protection After One Dose. Front. Immunol. 2020, 11, 304.

127. Taylor, A.; Liu, X.; Zaid, A.; Goh, L.Y.; Hobson-Peters, J.; Hall, R.A.; Merits, A.; Mahalingam, S. Mutation of the N-Termi nal Region of Chikungunya Virus Capsid Protein: Implications for Vaccine Design. mBio 2017, 8, e01970-16.

128. Kistner, O.; Barrett, N.; Bruhmann, A.; Reiter, M.; Mundt, W.; Savidis-Dacho, H.; Schober-Bendixen, S.; Dorner, F.; Aask ov, J. The preclinical testing of a formaldehyde inactivated Ross River virus vaccine designed for use in humans. Vacci ne 2007, 25, 4845–4852.

129. Aichinger, G.; Ehrlich, H.J.; Aaskov, J.G.; Fritsch, S.; Thomasser, C.; Draxler, W.; Wolzt, M.; Muller, M.; Pinl, F.; Van Da mme, P.; et al. Safety and immunogenicity of an inactivated whole virus Vero cell-derived Ross River virus vaccine: A ra ndomized trial. Vaccine 2011, 29, 9376–9384.

130. Chan, Y.H.; Teo, T.H.; Utt, A.; Tan, J.J.; Amrun, S.N.; Abu Bakar, F.; Yee, W.-X.; Becht, E.; Lee, C.Y.-P.; Lee, B.; et al. M utating chikungunya virus non-structural protein produces potent live-attenuated vaccine candidate. EMBO Mol. Med. 2 019, 11, e10092.

131. Hallengard, D.; Kakoulidou, M.; Lulla, A.; Kummerer, B.M.; Johansson, D.X.; Mutso, M.; Lulla, V.; Fazakerley, J.K.; Roq ues, P.; Le Grand, R.; et al. Novel attenuated Chikungunya vaccine candidates elicit protective immunity in C57BL/6 mi ce. J. Virol. 2014, 88, 2858–2866.

132. Roques, P.; Ljungberg, K.; Kummerer, B.M.; Gosse, L.; Dereuddre-Bosquet, N.; Tchitchek, N.; Hallengard, D.; Garcia-A rriaza, J.; Meinke, A.; Esteban, M.; et al. Attenuated and vectored vaccines protect nonhuman primates against Chikun gunya virus. JCI Insight 2017, 2, e83527.

133. Wressnigg, N.; Hochreiter, R.; Zoihsl, O.; Fritzer, A.; Bezay, N.; Klingler, A.; Lingnau, K.; Schneider, M.; Lundberg, U.; M einke, A.; et al. Single-shot live-attenuated chikungunya vaccine in healthy adults: A phase 1, randomised controlled tri al. Lancet Infect. Dis. 2020, 20, 1193–1203.

134. Carrau, L.; Rezelj, V.V.; Noval, M.G.; Levi, L.I.; Megrian, D.; Blanc, H.; Weger-Lucarelli, J.; Moratorio, G.; Stapleford, K. A.; Vignuzzi, M. Chikungunya Virus Vaccine Candidates with Decreased Mutational Robustness Are Attenuated In Vivo and Have Compromised Transmissibility. J. Virol. 2019, 93, e00775-19.

135. Piper, A.; Ribeiro, M.; Smith, K.M.; Briggs, C.M.; Huitt, E.; Nanda, K.; Spears, C.J.; Quiles, M.; Cullen, J.; Thomas, M. E.; et al. Chikungunya virus host range E2 transmembrane deletion mutants induce protective immunity against challen ge in C57BL/6J mice. J. Virol. 2013, 87, 6748–6757.

136. Gardner, C.L.; Hritz, J.; Sun, C.; Vanlandingham, D.L.; Song, T.Y.; Ghedin, E.; Higgs, S.; Klimstra, W.B.; Ryman, K.D. D eliberate attenuation of chikungunya virus by adaptation to heparan sulfate-dependent infectivity: A model for rational a rboviral vaccine design. PLoS Negl. Trop. Dis. 2014, 8, e2719.

137. Ludwig, G.V.; Turell, M.J.; Vogel, P.; Kondig, J.P.; Kell, W.K.; Smith, J.F.; Pratt, W.D. Comparative neurovirulence of atte nuated and non-attenuated strains of Venezuelan equine encephalitis virus in mice. Am. J. Trop. Med. Hyg. 2001, 64, 4 9–55.

138. Reed, D.S.; Lind, C.M.; Lackemeyer, M.G.; Sullivan, L.J.; Pratt, W.D.; Parker, M.D. Genetically engineered, live, attenu ated vaccines protect nonhuman primates against aerosol challenge with a virulent IE strain of Venezuelan equine enc ephalitis virus. Vaccine 2005, 23, 3139–3147.

139. Fine, D.L.; Roberts, B.A.; Terpening, S.J.; Mott, J.; Vasconcelos, D.; House, R.V. Neurovirulence evaluation of Venezue lan equine encephalitis (VEE) vaccine candidate V3526 in nonhuman primates. Vaccine 2008, 26, 3497–3506.

140. Main, C.F.D.; Snow, D.; Mallory, R.M.; Helber, S.; Terpening, S.; Holley, H.P. Safety of an Attenuated Venezuelan Equin e Encephalitis Virus (VEEV) Vaccine in Humans. In Proceedings of the America Infectious Diseases Society of America 2008 Annual Meeting, Washington, DC, USA, 25–28 October 2008.

141. Tretyakova, I.; Tibbens, A.; Jokinen, J.D.; Johnson, D.M.; Lukashevich, I.S.; Pushko, P. Novel DNA-launched Venezuel an equine encephalitis virus vaccine with rearranged genome. Vaccine 2019, 37, 3317–3325.

142. Tretyakova, I.; Plante, K.S.; Rossi, S.L.; Lawrence, W.S.; Peel, J.E.; Gudjohnsen, S.; Wang, E.; Mirchandani, D.; Tibbe ns, A.; Lamichhane, T.N.; et al. Venezuelan equine encephalitis vaccine with rearranged genome resists reversion and protects non-human primates from viremia after aerosol challenge. Vaccine 2020, 38, 3378–3386.

143. Trobaugh, D.W.; Sun, C.; Dunn, M.D.; Reed, D.S.; Klimstra, W.B. Rational design of a live-attenuated eastern equine e ncephalitis virus vaccine through informed mutation of virulence determinants. PLoS Pathog. 2019, 15, e1007584.

144. Plante, K.; Wang, E.; Partidos, C.D.; Weger, J.; Gorchakov, R.; Tsetsarkin, K.; Borland, E.M.; Powers, A.M.; Seymour, R.; Stinchcomb, D.T.; et al. Novel chikungunya vaccine candidate with an IRES-based attenuation and host range alter ation mechanism. PLoS Pathog. 2011, 7, e1002142.

145. Roy, C.J.; Adams, A.P.; Wang, E.; Plante, K.; Gorchakov, R.; Seymour, R.L.; Vinet-Oliphant, H.; Weaver, S.C. Chikungunya vaccine candidate is highly attenuated and protects nonhuman primates against telemetrically monitored disease following a single dose. J. Infect. Dis. 2014, 209, 1891–1899.

146. Partidos, C.D.; Paykel, J.; Weger, J.; Borland, E.M.; Powers, A.M.; Seymour, R.; Weaver, S.C.; Stinchcomb, D.T.; Osorio, J.E. Cross-protective immunity against o'nyong-nyong virus afforded by a novel recombinant chikungunya vaccine. Vaccine 2012, 30, 4638–4643.

147. Pandya, J.; Gorchakov, R.; Wang, E.; Leal, G.; Weaver, S.C. A vaccine candidate for eastern equine encephalitis virus based on IRES-mediated attenuation. Vaccine 2012, 30, 1276–1282.

148. Rossi, S.L.; Guerbois, M.; Gorchakov, R.; Plante, K.S.; Forrester, N.L.; Weaver, S.C. IRES-based Venezuelan equine encephalitis vaccine candidate elicits protective immunity in mice. Virology 2013, 437, 81–88.

149. Rossi, S.L.; Russell-Lodrigue, K.E.; Killeen, S.Z.; Wang, E.; Leal, G.; Bergren, N.A.; Vinet-Oliphant, H.; Weaver, S.C. IRES-Containing VEEV Vaccine Protects Cynomolgus Macaques from IE Venezuelan Equine Encephalitis Virus Aerosol Challenge. PLoS Negl. Trop. Dis. 2015, 9, e0003797.

150. Guerbois, M.; Volkova, E.; Forrester, N.L.; Rossi, S.L.; Frolov, I.; Weaver, S.C. IRES-driven expression of the capsid protein of the Venezuelan equine encephalitis virus TC-83 vaccine strain increases its attenuation and safety. PLoS Negl. Trop. Dis. 2013, 7, e2197.

151. Mota, M.T.O.; Costa, V.V.; Sugimoto, M.A.; Guimaraes, G.F.; Queiroz, C.M., Jr.; Moreira, T.P.; de Sousa, C.D.; Santos, F.M.; Queiroz, V.F.; Passos, I.; et al. In-depth characterization of a novel live-attenuated Mayaro virus vaccine candidate using an immunocompetent mouse model of Mayaro disease. Sci. Rep. 2020, 10, 5306.

152. Weise, W.J.; Hermance, M.E.; Forrester, N.; Adams, A.P.; Langsjoen, R.; Gorchakov, R.; Wang, E.; Alcorn, M.D.H.; Tsetsarkin, K.; Weaver, S.C. A novel live-attenuated vaccine candidate for mayaro Fever. PLoS Negl. Trop. Dis. 2014, 8, e2969.

153. Tiwari, M.; Parida, M.; Santhosh, S.R.; Khan, M.; Dash, P.K.; Rao, P.V. Assessment of immunogenic potential of Vero adapted formalin inactivated vaccine derived from novel ECSA genotype of Chikungunya virus. Vaccine 2009, 27, 2513–2522.

154. Kumar, M.; Sudeep, A.B.; Arankalle, V.A. Evaluation of recombinant E2 protein-based and whole-virus inactivated candidate vaccines against chikungunya virus. Vaccine 2012, 30, 6142–6149.

155. Mohan, K. Phase-I Open Label, Dose-Escalation Clinical Trial to Evaluate the Safety, Tolerability and Immunogenicity of Chikungunya Vaccine in Healthy Adults of 18 to 50 Years Age: U.S National Library of Medicine. 2020. Available online: (accessed on 18 March 2021).

156. Pittman, P.R.; Liu, C.T.; Cannon, T.L.; Mangiafico, J.A.; Gibbs, P.H. Immune interference after sequential alphavirus vaccine vaccinations. Vaccine 2009, 27, 4879–4882.

157. Maryam, K.-J.; Reisler, R.B.; Purcell, B.K.; Rivard, R.G.; Cardile, A.P.; Liggett, D.; Norris, S.; Pitttman, P.R. 2773. Safety and Immunogenicity Study of Eastern Equine Encephalitis Vaccine. Open Forum Infect. Dis. 2019, 6, 978–979.

158. Rivard, R. Phase 2 Open-Label Safety and Immunogenicity Study of the Eastern Equine Encephalitis (EEE) Vaccine, Inactivated, Dried, TSI-GSD 104, Lot 2-1-89, in Healthy Adult Subjects at Risk of Exposure to Eastern Equine Encephalitis Virus: U.S. National Library of Medicine. 2016. Available online: (accessed on 18 March 2021).

159. Honnold, S.P.; Bakken, R.R.; Fisher, D.; Lind, C.M.; Cohen, J.W.; Eccleston, L.T.; Spurgers, K.B.; Maheshwari, R.K.; Glass, P.J. Second generation inactivated eastern equine encephalitis virus vaccine candidates protect mice against a lethal aerosol challenge. PLoS ONE 2014, 9, e104708.

160. Martin, S.S.; Bakken, R.R.; Lind, C.M.; Garcia, P.; Jenkins, E.; Glass, P.J.; Parker, M.D.; Hart, M.K.; Fine, D.L. Evaluation of formalin inactivated V3526 virus with adjuvant as a next generation vaccine candidate for Venezuelan equine encephalitis virus. Vaccine 2010, 28, 3143–3151.

161. Gupta, P.; Sharma, A.; Spurgers, K.B.; Bakken, R.R.; Eccleston, L.T.; Cohen, J.W.; Honnold, S.P.; Glass, P.J.; Maheshwari, R.K. 1,5-Iodonaphthyl azide-inactivated V3526 protects against aerosol challenge with virulent venezuelan equine encephalitis virus. Vaccine 2016, 34, 2762–2765.

162. Fine, D.L.; Jenkins, E.; Martin, S.S.; Glass, P.; Parker, M.D.; Grimm, B. A multisystem approach for development and evaluation of inactivated vaccines for Venezuelan equine encephalitis virus (VEEV). J. Virol. Method. 2010, 163, 424–432.

163. McCarty, J. A Phase 2 Parallel-Group, Randomized, Double-Blind Study to Assess the Safety and Immunogenicity of PXVX0317 (Chikungunya Virus Virus-Like Particle Vaccine [CHIKV-VLP], Unadjuvanted or Alum-adjuvanted): U.S. National Library of Medicine. 2018. Available online: (accessed on 18 March 2021).

164. Metz, S.W.; Martina, B.E.; van den Doel, P.; Geertsema, C.; Osterhaus, A.D.; Vlak, J.M.; Pijlman, G.P. Chikungunya virus-like particles are more immunogenic in a lethal AG129 mouse model compared to glycoprotein E1 or E2 subunits. Vaccine 2013, 31, 6092–6096.

165. Metz, S.W.; Gardner, J.; Geertsema, C.; Le, T.T.; Goh, L.; Vlak, J.M.; Pijlman, G.P. Effective chikungunya virus-like particle vaccine produced in insect cells. PLoS Negl. Trop. Dis. 2013, 7, e2124.

166. Saraswat, S.; Athmaram, T.N.; Parida, M.; Agarwal, A.; Saha, A.; Dash, P.K. Expression and Characterization of Yeast Derived Chikungunya Virus Like Particles (CHIK-VLPs) and Its Evaluation as a Potential Vaccine Candidate. PLoS Neg

l. Trop. Dis. 2016, 10, e0004782.

167. Goonewardena, S. A Phase 1 Dose Escalation Study to Assess the Safety and Immunogenicity of a Monovalent Virus-Like Particle (VLP) Venezuelan Equine Encephalitis Vaccine in Healthy Adults: U.S. National Library of Medicine. 2017. Available online: (accessed on 18 March 2021).

168. Ko, S.Y.; Akahata, W.; Yang, E.S.; Kong, W.P.; Burke, C.W.; Honnold, S.P.; Nichols, D.K.; Huang, Y.-J.S.; Schieber, G. L.; Carlton, K.; et al. A virus-like particle vaccine prevents equine encephalitis virus infection in nonhuman primates. Sc i. Transl. Med. 2019, 11, 492.

169. Ledgerwood, J.C.G. A Phase 1 Open Label, Dose-Escalation Clinical Trial to Evaluate the Safety and Immunogenicity of a Trivalent Virus-Like Particle (VLP) Encephalitis Vaccine, VRC-WEVVLP073-00-VP, in Healthy Adults: U.S. National Library of Medicine. 2019. Available online: (accessed on 18 March 2021).

170. Riemenschneider, J.; Garrison, A.; Geisbert, J.; Jahrling, P.; Hevey, M.; Negley, D.; Schmaljohn, A.; Lee, J.; Hart, M.K.; Vanderzanden, L.; et al. Comparison of individual and combination DNA vaccines for B. anthracis, Ebola virus, Marburg virus and Venezuelan equine encephalitis virus. Vaccine 2003, 21, 4071–4080.

171. Hart, M.K.; Pratt, W.; Panelo, F.; Tammariello, R.; Dertzbaugh, M. Venezuelan equine encephalitis virus vaccines induc e mucosal IgA responses and protection from airborne infection in BALB/c, but not C3H/HeN mice. Vaccine 1997, 15, 3 63–369.

172. Perkins, S.D.; O'Brien, L.M.; Phillpotts, R.J. Boosting with an adenovirus-based vaccine improves protective efficacy ag ainst Venezuelan equine encephalitis virus following DNA vaccination. Vaccine 2006, 24, 3440–3445.

173. Dupuy, L.C.; Locher, C.P.; Paidhungat, M.; Richards, M.J.; Lind, C.M.; Bakken, R.; Parker, M.D.; Wahlen, R.G.; Schmalj ohn, C.S. Directed molecular evolution improves the immunogenicity and protective efficacy of a Venezuelan equine en cephalitis virus DNA vaccine. Vaccine 2009, 27, 4152–4160.

174. Tretyakova, I.; Lukashevich, I.S.; Glass, P.; Wang, E.; Weaver, S.; Pushko, P. Novel vaccine against Venezuelan equin e encephalitis combines advantages of DNA immunization and a live attenuated vaccine. Vaccine 2013, 31, 1019–102 5.

175. Gauci, P.J.; Wu, J.Q.; Rayner, G.A.; Barabe, N.D.; Nagata, L.P.; Proll, D.F. Identification of Western equine encephalitis virus structural proteins that confer protection after DNA vaccination. Clin. Vaccine Immunol. 2010, 17, 176–179.

176. Muthumani, K.; Lankaraman, K.M.; Laddy, D.J.; Sundaram, S.G.; Chung, C.W.; Sako, E.; Wu, L.; Khan, A.; Sardesai, N.; Kim, J.J.; et al. Immunogenicity of novel consensus-based DNA vaccines against Chikungunya virus. Vaccine 2008, 26, 5128–5134.

177. Bao, H.; Ramanathan, A.A.; Kawalakar, O.; Sundaram, S.G.; Tingey, C.; Bian, C.B.; Muruganandam, N.; Vijauachari, P.; Sardesai, N.Y.; Weiner, D.B.; et al. Nonstructural protein 2 (nsP2) of Chikungunya virus (CHIKV) enhances protectiv e immunity mediated by a CHIKV envelope protein expressing DNA Vaccine. Viral Immunol. 2013, 26, 75–83.

178. Mallilankaraman, K.; Shedlock, D.J.; Bao, H.; Kawalekar, O.U.; Fagone, P.; Ramanathan, A.A.; Ferraro, B.; Stabenow, J.; Vijayachari, P.; Sundaran, S.G.; et al. A DNA vaccine against chikungunya virus is protective in mice and induces ne utralizing antibodies in mice and nonhuman primates. PLoS Negl. Trop. Dis. 2011, 5, e928.

179. Dupuy, L.C.; Richards, M.J.; Livingston, B.D.; Hannaman, D.; Schmaljohn, C.S. A Multiagent Alphavirus DNA Vaccine D elivered by Intramuscular Electroporation Elicits Robust and Durable Virus-Specific Immune Responses in Mice and Ra bbits and Completely Protects Mice against Lethal Venezuelan, Western, and Eastern Equine Encephalitis Virus Aeros ol Challenges. J. Immunol. Res. 2018, 2018, 8521060.

180. Choi, H.; Kudchodkar, S.B.; Reuschel, E.L.; Asija, K.; Borole, P.; Ho, M.; Wojtak, K.; Reed, C.; Ramos, S.; Bopp, N.E.; et al. Protective immunity by an engineered DNA vaccine for Mayaro virus. PLoS Negl. Trop. Dis. 2019, 13, e0007042.

181. Tretyakova, I.; Hearn, J.; Wang, E.; Weaver, S.; Pushko, P. DNA vaccine initiates replication of live attenuated chikungu nya virus in vitro and elicits protective immune response in mice. J. Infect. Dis. 2014, 209, 1882–1890.

182. Muthumani, K.; Block, P.; Flingai, S.; Muruganantham, N.; Chaaithanya, I.K.; Tingey, C.; Wise, M.; Reuschel, E.L.; Chu ng, C.; Muthumani, A.; et al. Rapid and Long-Term Immunity Elicited by DNA-Encoded Antibody Prophylaxis and DNA Vaccination Against Chikungunya Virus. J. Infect. Dis. 2016, 214, 369–378.

183. Szurgot, I.; Ljungberg, K.; Kummerer, B.M.; Liljestrom, P. Infectious RNA vaccine protects mice against chikungunya vir us infection. Sci. Rep. 2020, 10, 21076.

184. Dupuy, L.C.; Richards, M.J.; Ellefsen, B.; Chau, L.; Luxembourg, A.; Hannaman, D.; Livingston, B.D.; Schmaljohn, C.S. A DNA vaccine for venezuelan equine encephalitis virus delivered by intramuscular electroporation elicits high levels of neutralizing antibodies in multiple animal models and provides protective immunity to mice and nonhuman primates. Cli n. Vaccine Immunol. 2011, 18, 707–716.

185. Hannaman, D.; Dupuy, L.C.; Ellefsen, B.; Schmaljohn, C.S. A Phase 1 clinical trial of a DNA vaccine for Venezuelan eq uine encephalitis delivered by intramuscular or intradermal electroporation. Vaccine 2016, 34, 3607–3612.

186. Nagata, L.P.; Hu, W.G.; Masri, S.A.; Rayner, G.A.; Schmaltz, F.L.; Das, D.; Wu, J.; Long, M.C.; Chan, C.; Proll, D.; et al. Efficacy of DNA vaccination against western equine encephalitis virus infection. Vaccine 2005, 23, 2280–2283.

187. Phillips, A.T.; Schountz, T.; Toth, A.M.; Rico, A.B.; Jarvis, D.L.; Powers, A.M.; Olson, K.E. Liposome-antigen-nucleic aci d complexes protect mice from lethal challenge with western and eastern equine encephalitis viruses. J. Virol. 2014, 8 8, 1771–1780.

188. Shaw, C.; Panther, L.; August, A.; Zaks, T.; Smolenov, I.; Bart, S.; Watson, M. Safety and immunogenicity of a mRNA-based chikungunya vaccine in a phase 1 dose-ranging trial. Int. J. Infect. Dis. 2019, 79, 17.

189. Kose, N.; Fox, J.M.; Sapparapu, G.; Bombardi, R.; Tennekoon, R.N.; de Silva, A.D.; Elbashir, S.M.; Theisen, M.A.; Humphris-Narayanan, E.; Ciaramella, G.; et al. A lipid-encapsulated mRNA encoding a potently neutralizing human monoclonal antibody protects against chikungunya infection. Sci. Immunol. 2019, 4, eaaw6647.

190. Moderna, T.X. A Phase 1, Randomized, Placebo-Controlled, Dose Ranging Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of mRNA-1944, Encoding for an Anti-Chikungunya Virus Monoclonal Antibody, in Healthy Adults: U.S. National Library of Medicine. 2019. Available online: (accessed on 18 March 2021).

191. Metz, S.W.; Geertsema, C.; Martina, B.E.; Andrade, P.; Heldens, J.G.; van Oers, M.M.; Goldbach, R.W.; Vlak, J.M.; Pijlman, G.P. Functional processing and secretion of Chikungunya virus E1 and E2 glycoproteins in insect cells. Virol. J. 2011, 8, 353.

192. Khan, M.; Dhanwani, R.; Rao, P.V.; Parida, M. Subunit vaccine formulations based on recombinant envelope proteins of Chikungunya virus elicit balanced Th1/Th2 response and virus-neutralizing antibodies in mice. Virus Res. 2012, 167, 236–246.

193. Brandler, S.; Ruffie, C.; Combredet, C.; Brault, J.B.; Najburg, V.; Prevost, M.C.; Habel, A.; Tauber, E.; Despres, P.; Tangy, F. A recombinant measles vaccine expressing chikungunya virus-like particles is strongly immunogenic and protects mice from lethal challenge with chikungunya virus. Vaccine 2013, 31, 3718–3725.

194. Gerke, C.; Frantz, P.N.; Ramsauer, K.; Tangy, F. Measles-vectored vaccine approaches against viral infections: A focus on Chikungunya. Expert Rev. Vaccines 2019, 18, 393–403.

195. Rossi, S.L.; Comer, J.E.; Wang, E.; Azar, S.R.; Lawrence, W.S.; Plante, J.A.; Ramsauer, K.; Schrauf, S.; Weaver, S.C. Immunogenicity and Efficacy of a Measles Virus-Vectored Chikungunya Vaccine in Nonhuman Primates. J. Infect. Dis. 2019, 220, 735–742.

196. Ramsauer, K.; Schwameis, M.; Firbas, C.; Mullner, M.; Putnak, R.J.; Thomas, S.J.; Despres, P.; Tauber, E.; Jilma, B.; Tangy, F. Immunogenicity, safety, and tolerability of a recombinant measles-virus-based chikungunya vaccine: A randomised, double-blind, placebo-controlled, active-comparator, first-in-man trial. Lancet Infect. Dis. 2015, 15, 519–527.

197. Reisinger, E.C.; Tschismarov, R.; Beubler, E.; Wiedermann, U.; Firbas, C.; Loebermann, M.; Pfeiffer, A.; Muellner, M.; Tauber, E.; Ramsauer, L. Immunogenicity, safety, and tolerability of the measles-vectored chikungunya virus vaccine MV-CHIK: A double-blind, randomised, placebo-controlled and active-controlled phase 2 trial. Lancet 2019, 392, 2718–2727.

198. Wang, E.; Volkova, E.; Adams, A.P.; Forrester, N.; Xiao, S.Y.; Frolov, I.; Weaver, S.C. Chimeric alphavirus vaccine candidates for chikungunya. Vaccine 2008, 26, 5030–5039.

199. Wang, E.; Kim, D.Y.; Weaver, S.C.; Frolov, I. Chimeric Chikungunya viruses are nonpathogenic in highly sensitive mouse models but efficiently induce a protective immune response. J. Virol. 2011, 85, 9249–9252.

200. Wang, E.; Petrakova, O.; Adams, A.P.; Aguilar, P.V.; Kang, W.; Paessler, S.; Volk, S.M.; Frolov, I.; Weaver, S.C. Chimeric Sindbis/eastern equine encephalitis vaccine candidates are highly attenuated and immunogenic in mice. Vaccine 2007, 25, 7573–7581.

201. Paessler, S.; Fayzulin, R.Z.; Anishchenko, M.; Greene, I.P.; Weaver, S.C.; Frolov, I. Recombinant sindbis/Venezuelan equine encephalitis virus is highly attenuated and immunogenic. J. Virol. 2003, 77, 9278–9286.

202. Paessler, S.; Ni, H.; Petrakova, O.; Fayzulin, R.Z.; Yun, N.; Anishchenko, M.; Weaver, S.C.; Frolov, I. Replication and clearance of Venezuelan equine encephalitis virus from the brains of animals vaccinated with chimeric SIN/VEE viruses. J. Virol. 2006, 80, 2784–2796.

203. Atasheva, S.; Wang, E.; Adams, A.P.; Plante, K.S.; Ni, S.; Taylor, K.; Miller, M.E.; Frolov, I.; Weaver, S.C. Chimeric alphavirus vaccine candidates protect mice from intranasal challenge with western equine encephalitis virus. Vaccine 2009, 27, 4309–4319.

204. Garcia-Arriaza, J.; Cepeda, V.; Hallengard, D.; Sorzano, C.O.; Kummerer, B.M.; Liljestrom, P.; Esteban, M. A novel poxvirus-based vaccine, MVA-CHIKV, is highly immunogenic and protects mice against chikungunya infection. J. Virol. 2014, 88, 3527–3547.

205. Weger-Lucarelli, J.; Chu, H.; Aliota, M.T.; Partidos, C.D.; Osorio, J.E. A novel MVA vectored Chikungunya virus vaccine elicits protective immunity in mice. PLoS Negl. Trop. Dis. 2014, 8, e2970.

206. Van den Doel, P.; Volz, A.; Roose, J.M.; Sewbalaksing, V.D.; Pijlman, G.P.; van Middelkoop, I.; Duiverman, V.; van de Wetering, E.; Sutter, G.; Osterhaus, A.D.M.E.; et al. Recombinant modified vaccinia virus Ankara expressing glycoprotein E2 of Chikungunya virus protects AG129 mice against lethal challenge. PLoS Negl. Trop. Dis. 2014, 8, e3101.

207. Hu, W.G.; Steigerwald, R.; Kalla, M.; Volkmann, A.; Noll, D.; Nagata, L.P. Protective efficacy of monovalent and trivalent recombinant MVA-based vaccines against three encephalitic alphaviruses. Vaccine 2018, 36, 5194–5203.

208. Wang, D.; Suhrbier, A.; Penn-Nicholson, A.; Woraratanadharm, J.; Gardner, J.; Luo, M.; Le, T.T.; Anraku, I.; Sakalian, M.; Einfeld, D.; et al. A complex adenovirus vaccine against chikungunya virus provides complete protection against viraemia and arthritis. Vaccine 2011, 29, 2803–2809.

209. Lopez-Camacho, C.; Kim, Y.C.; Blight, J.; Lazaro Moreli, M.; Montoya-Diaz, E.; Huiskonen, J.T.; Kummerer, B.M.; Reyes-Sandoval, A. Assessment of Immunogenicity and Neutralisation Efficacy of Viral-Vectored Vaccines Against Chikungu

nya Virus. Viruses 2019, 11, 322.

210. Kroon Campos, R.; Preciado-Llanes, L.; Azar, S.R.; Kim, Y.C.; Brandon, O.; Lopez-Camacho, C.; Reyes-Sandoval, A.; Rossi, S.L. Adenoviral-Vectored Mayaro and Chikungunya Virus Vaccine Candidates Afford Partial Cross-Protection Fr om Lethal Challenge in A129 Mouse Model. Front. Immunol. 2020, 11, 591885.
211. Campos, R.K.; Preciado-Llanes, L.; Azar, S.R.; Lopez-Camacho, C.; Reyes-Sandoval, A.; Rossi, S.L. A Single and Un-Adjuvanted Dose of a Chimpanzee Adenovirus-Vectored Vaccine against Chikungunya Virus Fully Protects Mice from L ethal Disease. Pathogens 2019, 8, 231.
212. Hill, A.V. Safety and Immunogenicity of a Candidate CHIKV Vaccine (CHIK001): National Library of Medicine (U.S.). 20 18. Available online: (accessed on 18 March 2021).
213. Phillpotts, R.J.; O'Brien, L.; Appleton, R.E.; Carr, S.; Bennett, A. Intranasal immunisation with defective adenovirus sero type 5 expressing the Venezuelan equine encephalitis virus E2 glycoprotein protects against airborne challenge with vir ulent virus. Vaccine 2005, 23, 1615–1623.
214. Perkins, S.D.; Williams, A.J.; O'Brien, L.M.; Laws, T.R.; Phillpotts, R.J. CpG used as an adjuvant for an adenovirus-bas ed Venezuelan equine encephalitis virus vaccine increases the immune response to the vector, but not to the transgen e product. Viral. Immunol. 2008, 21, 451–457.
215. Wu, J.Q.; Barabe, N.D.; Chau, D.; Wong, C.; Rayner, G.R.; Hu, W.G.; Nagata, L.P. Complete protection of mice against a lethal dose challenge of western equine encephalitis virus after immunization with an adenovirus-vectored vaccine. V accine 2007, 25, 4368–4375.
216. Swayze, R.D.; Bhogal, H.S.; Barabe, N.D.; McLaws, L.J.; Wu, J.Q. Envelope protein E1 as vaccine target for western e quine encephalitis virus. Vaccine 2011, 29, 813–820.
217. Chattopadhyay, A.; Wang, E.; Seymour, R.; Weaver, S.C.; Rose, J.K. A chimeric vesiculo/alphavirus is an effective alph avirus vaccine. J. Virol. 2013, 87, 395–402.
218. Nasar, F.; Matassov, D.; Seymour, R.L.; Latham, T.; Gorchakov, R.V.; Nowak, R.M.; Leal, G.; Hamm, S.; Eldridge, J.H.; Tesh, R.B.; et al. Recombinant Isfahan Virus and Vesicular Stomatitis Virus Vaccine Vectors Provide Durable, Multivale nt, Single-Dose Protection against Lethal Alphavirus Challenge. J. Virol. 2017, 91, e01729-16.
219. Fierro, C. Phase 1 Vaccination Trial to Evaluate Safety, Tolerability and Immunogenicity of a Recombinant MVA-BN-WE V Vaccine in Healthy Adult Subjects: National Library of Medicine (U.S.). 2019. Available online: (accessed on 18 Marc h 2021).
220. Erasmus, J.H.; Auguste, A.J.; Kaelber, J.T.; Luo, H.; Rossi, S.L.; Fenton, K.; Leal, G.; Kim, D.Y.; Chiu, W.; Wang, T.; et al. A chikungunya fever vaccine utilizing an insect-specific virus platform. Nat. Med. 2017, 23, 192–199.